The Journal of Allergy

VOL. 10 JANUARY, 1939 No. 2

Original Articles

FOOD ALLERGENS*

II. ATOPIC REAGINS AND THE BOTANICAL CLASSIFICATION OF FOODS

ORVAL R. WITHERS, M.D.
KANSAS CITY, MO.

VAUGHAN,[1] and later, Ellis[2] grouped certain foods into a genetic classification and suggested that clinical hypersensitiveness would occur according to this grouping.

Baldwin and Benedict[3] have shown close relationship of atopic reagins in botanically related vegetable foods. According to these investigators it may be presumed that reagins are present when the patient is clinically sensitive, and there are marked skin reactions to the same food. It also appears that the reagins may be present in food-sensitive patients who are not clinically sensitive, as shown by Chobot and Herwitz,[4] Peshkin[5] and others.

The purpose of this paper is to correlate the clinical reactions with skin tests and with atopic reagins to the various foods in certain botanical families, as well as to determine whether there are reagins in the blood to botanically related foods.

Twenty patients were selected who had been proved clinically sensitive to the foods in one or more of seven botanical families; 8 were male and 12 female; their ages ranged from 18 to 72 years. Although the allergic manifestations were multiple, the chief ailments were chronic vasomotor rhinitis, bronchial asthma, one or both; 3 had secondary allergic conditions, such as headache, gastrointestinal allergy, angioneurotic edema, and urticaria. Ten were clinically sensitive to pollen.

METHOD

Blood was drawn into a dry syringe and placed in a sterile centrifuge tube, permitted to clot, then centrifuged, and the serum drawn off and passed through a Seitz filter. Recipients employed were young normal adults with a negative allergic history who showed no skin reactions

*From the Allergy Clinic of the Department of Medicine, University of Kansas School of Medicine.

Read before the Annual Meeting of the Association for the Study of Allergy, San Francisco, Calif., June 10, 1938.

to the allergenic extracts. Lederle's allergenic extracts were used on patients and recipients, and all tests were made by the intracutaneous method. Each food sensitive patient was retested immediately after sufficient blood had been drawn for passive transfer, and skin sensitivity by direct testing was determined for each food in a botanical family in which the patient showed clinical sensitivity. The recipients did not eat the foods in the botanical families to be transferred forty-eight hours prior to the preparation of the sensitized areas. One-tenth of a cubic centimeter of serum was used to prepare each skin site, and forty-eight hours later it was tested with 0.02 c.c. of the food extract. Each site was tested only once. To avoid refractory areas, the control tests were placed at least 2 inches laterally and between sensitized areas which were never closer than 1½ inches.

All of the patients had been under observation from six months to two years, and their clinical sensitivities were determined by repeated deliberate feedings of the suspected food.

RESULTS

Although 7 botanical families were used in this investigation, only 3 families will be considered in detail. Twenty patients were clinically sensitive to foods of the 7 families, 10 reacted to cereals, 13 to legumes, and 14 to the tomato family.

Cereal Family.—Ten patients showed a total of 24 positive clinical reactions to 6 members of the cereal group. Nine reacted to wheat, 5 to rye, 2 to barley, 3 to corn, 2 to oats, and 3 to rice. Of the 9 patients clinically sensitive to wheat, 3 showed a positive skin reaction and a positive passive transfer. The remaining 6 clinically wheat-sensitive patients were skin negative and passive transfer negative. One patient, not clinically sensitive to wheat but clinically sensitive to other members of the cereal family, was negative to direct and indirect testing to wheat.

Five patients were clinically sensitive to rye, and 4 reacted with a positive skin test; 2 of these showed a positive and 2 a negative passive transfer. The fifth patient, although clinically sensitive, showed a negative response both to direct and indirect testing. Of the 5 patients not clinically sensitive to rye, 2 showed positive skin reactions, and one a positive passive transfer. The remaining 3 patients were negative to both tests with rye.

Two patients were clinically sensitive to barley; one showed a positive skin reaction and a positive passive transfer and the other did not. Of the 8 patients not clinically sensitive to barley, 6 were negative both by direct and indirect testing, while 2 gave a positive direct skin test, and one of these a positive indirect reaction to barley.

Of the 3 patients clinically sensitive to corn meal, 2 gave negative skin reactions and passive transfers, while the third reacted both to direct skin testing and passive transfer. Seven patients were clinically nega-

tive to corn meal; 3 of these were negative by skin test and also passive transfer. The remaining 4 reacted with a positive skin test, and 2 showed a positive passive transfer to corn meal.

Two patients were clinically sensitive to oats; one showed a positive skin test and also a positive passive transfer; the second patient was negative to both tests. Of the 8 patients clinically negative to oats, 4 were negative by direct and indirect testing; the other 4 showed a positive skin test, and 2 of these showed a positive passive transfer to oats.

Three patients were clinically sensitive to rice; one showed a positive passive transfer, while the other 2 were negative for both of these tests. The 7 patients not clinically sensitive to rice reacted as follows: 3 were negative both to direct and indirect testing, 3 showed only a positive passive transfer, but were skin negative to rice.

TABLE I

CEREAL FAMILY

	CLIN. POS.	CLIN. NEG.	CLIN. NOT TESTED	TOTAL P.T. TESTS
	10 Patients—60 Clinical Tests			
Skin neg. P.T. neg.	13	19	1	33
Skin pos. P.T. neg.	2	7	1	10
Skin neg. P.T. pos.	0	0	0	0
Skin pos. P.T. pos.	9	8	0	17
Total clinical reactions	24	34	2	60

Of the 60 clinical reactions, 24 were positive. Of this number 13 were skin and passive transfer negative; 9 showed a positive skin test and passive transfer; 2 showed a positive skin reaction only. Nineteen of the 34 clinically negative patients were also skin negative and passive transfer negative.

Legume Family.—The legume group is closely related both clinically and botanically. Thirteen patients showed a total of 46 positive clinical reactions to the 5 representative foods in this family. Eleven were clinically sensitive to green pea, 12 to navy bean, 11 to peanut, 9 to string bean, and 3 to soybean. There were 13 instances where the foods were not tested clinically, chiefly to soybean.

Of the 11 patients clinically sensitive to green pea, 5 failed to show a positive skin reaction, and none showed a positive passive transfer. Six other patients gave positive direct skin tests and one transferred. The 2 patients who were clinically negative to green pea were negative both to direct and indirect testing to the extract of this food.

Twelve patients were clinically sensitive to navy bean. Seven were skin negative to intradermal testing, and none showed a positive passive transfer. In 5 others there were positive skin tests, and 4 of these showed a positive passive transfer. One clinically negative patient did not show a positive skin reaction or passive transfer to navy bean.

Of 11 patients reacting to peanut, 6 were clinically sensitive only. Five patients showed a positive skin reaction, and in 4 the reagins

were transferable. Two patients failed to test peanuts clinically, but neither were positive on direct or indirect testing.

Three patients were clinically sensitive to soybean. One showed a positive skin reaction, while the other 2 showed both positive skin test and passive transfer. The clinical reaction was not determined in 10 patients sensitive to soybean, but 4 showed a positive direct skin reaction, and one of these gave a positive passive transfer. The remaining 6 were skin negative and did not transfer.

TABLE II

LEGUME FAMILY

	CLIN. POS.	CLIN. NEG.	CLIN. NOT TESTED	TOTAL P.T. TESTS
13 Patients—65 Clinical Tests				
Skin neg. P.T. neg.	22	4	9	35
Skin pos. P.T. neg.	10	1	3	14
Skin neg. P.T. pos.	0	0	0	0
Skin pos. P.T. pos.	14	1	1	16
Total clinical reactions	46	6	13	65

Twenty-two of the 46 clinically positive patients showed negative skin tests and negative passive transfer; 10 patients were skin positive, but showed negative passive transfer; the remaining 14 were both skin positive and passive transfer positive. Of the 6 clinically negative patients, only one showed a positive skin reaction and a negative passive transfer. Thirteen patients did not test the foods clinically.

Tomato Family.—The tomato family *(Solanaceae)* is not closely related clinically. Thirteen patients reacted with a total of 21 positive clinical sensitivities, 9 to tomato, 6 to Irish potato, 4 to green pepper, and 2 to eggplant. Of the 9 patients clinically sensitive to tomato, 5 were negative both to direct and indirect testing. Four were skin positive by direct test and 2 of these were positive on passive transfer. Of the 4 clinically negative patients, 2 showed positive skin tests and positive passive transfer to tomato and 2 did not.

Six patients were clinically sensitive to potato. Five were skin negative and passive transfer negative. The sixth gave a positive skin test and a positive passive transfer. Of the 8 patients not clinically sensitive to potato, but reacting to other members of this botanical family, 5 were negative both to direct and indirect testing. The remaining 3 showed positive skin tests, and 2 of them showed positive passive transfer.

Of the 4 patients clinically sensitive to green pepper, 4 gave a positive direct skin reaction, 3 of these a positive passive transfer. The 4 patients who had not tested green pepper clinically showed a positive skin reaction, and 2 of these were positive on passive transfer. Six patients were not clinically sensitive to green pepper. Four of these gave a positive skin reaction, 2 of whom showed a positive passive transfer. The fifth and sixth patients did not react to direct or indirect testing with green pepper.

Eight patients were skin sensitive to eggplant either by direct or indirect testing. Only 2 of these were clinically sensitive, while 6 had not tested eggplant clinically. Of the 2 clinically sensitive patients, one showed a positive skin test and passive transfer and the other did not. Six patients did not test eggplant clinically, but all of them showed a positive direct skin test, and 3 showed a positive passive transfer. Of the six patients not clinically sensitive to eggplant, 5 showed a positive skin reaction, and none a positive passive transfer. The sixth patient failed to show either a direct or indirect reaction.

TABLE III

TOMATO FAMILY

	CLIN. POS.	CLIN. NEG.	CLIN. NOT TESTED	TOTAL P.T. TESTS
	14 Patients—56 Clinical Tests			
Skin neg. P.T. neg.	10	11	0	21
Skin pos. P.T. neg.	4	7	5	16
Skin neg. P.T. pos.	0	0	0	0
Skin pos. P.T. pos.	7	7	5	19
Total clinical reactions	21	25	10	56

Of the 21 clinically positive reactions, 10 were skin negative and passive transfer negative; 7 showed a positive skin reaction and a positive passive transfer. Of the 25 patients clinically negative, but sensitive to other members of this group, 11 were skin and passive transfer negative; 7 showed a positive skin test and positive passive transfer. Ten patients did not test the foods clinically.

TABLE IV

	CLIN. POS.	CLIN. NEG.	UNDETERMINED	TOTAL CLINICAL TESTS
Skin neg. P.T. neg.	45 or 49 per cent	34 or 52 per cent	10	89
Skin pos. P.T. neg.	16 or 18 per cent	15 or 23 per cent	9	40
Skin neg. P.T. pos.	0	0	0	0
Skin pos. P.T. pos.	30 or 33 per cent	16 or 25 per cent	6	52
Total reactions	91	65	25	181

COMMENT

Table IV is a résumé of the clinical, direct and indirect reactions of the foods of three botanical families. They were selected because clinically, crossed sensitization is most pronounced in the bean family, to a less degree in the cereals, and least in the tomato family. Of the 181 possible clinical reactions, 91 were clinically positive and 65 clinically negative, while in 25 instances the food was not clinically tested. Of the 91 clinically positive reactions, 45, or 49 per cent, were negative both to direct and indirect testing. Sixteen, or 18 per cent, gave positive skin reactions and negative passive transfers. Thirty, or 33 per cent, were positive both to direct and indirect testing. Of the 65 clinically negative reactions, 34 patients, or 52 per cent, were negative both to direct and indirect testing; 15 patients, or 23.7 per cent, gave positive skin reactions and negative passive transfers; whereas 16 patients, or 25 per cent, were positive both to direct and indirect skin testing.

It appears that the sera of patients who are skin sensitive to one food and clinically sensitive to another in the same botanical family do not necessarily show reagins to either food. We have demonstrated that patients may be clinically sensitive to various foods in a botanical family with positive or negative skin tests and with positive or negative local passive transfer in almost any combination, except a skin negative reaction with a positive passive transfer.

The passive transfer, like the skin test, does not in any way indicate the degree of clinical sensitivity or the reacting time of the food tested. For example, one patient showed a questionable positive passive transfer reaction to green pea, and a marked passive transfer reaction to navy bean. Clinically, a mouthful of green peas causes a watery discharge and severe nasal blocking in less than fifteen minutes, and of two to four hours' duration, while a large helping of navy beans results in a very slight stuffiness after two or three hours, accompanied by thick tenacious mucus, which is more annoying than uncomfortable, and continues for twelve to eighteen hours.

In some instances a variation in the degree of passive transfer reactions was noted when the same sera were tested on more than one normal individual. The variation was not marked, usually from a plus-minus to a one-plus or a one- to two-plus reaction. This is explained as probably due to a slight difference in the receptivity of normal skin or as an experimental error.[6] The variation between sera containing the reagins of the same food is apparently dependent on the reagin titer.

It was noted in all pollen and food sensitive cases, that passive transfer to pollen was easier to obtain than passive transfer to food. A higher incidence of positive direct and indirect reactions may have resulted with a higher concentration of testing material. The fact that practically all foods to which these patients are clinically sensitive have been omitted from the diet from six months to two years may also be a factor in reducing the skin response.

The clinical reaction is more accurate in establishing group relationship or crossed clinical sensitization than the skin or passive transfer test. This does not indicate that an immunologic relationship does not exist, but that it has not been demonstrated by present methods. Baldwin and Benedict have shown the close relationship of atopens in botanically related foods in those clinically sensitive with marked positive skin tests. But what mechanism is involved in the clinically positive skin negative patients, or in the patients who are clinically negative but positive both to direct and indirect testing, is not determined.

SUMMARY

Sera of patients clinically sensitive and skin negative to one food, and clinically negative but skin positive to another in the same botanical family, may or may not contain atopic reagins.

These findings and conclusions coincide with those of Peshkin, Chobot, and Herwitz. However, our data were obtained from adults clinically sensitive to botanically related foods while their findings were obtained from children, and the investigation was not conducted from the standpoint of botanically related foods.

REFERENCES

1. Vaughan, Warren T.: J. ALLERGY **1**: 385, 1930.
2. Ellis, Ralph V.: J. ALLERGY **2**: 246, 1931.
3. Baldwin, Horace S., and Benedict, Mabel I.: J. ALLERGY **8**: 120, 1937.
4. Chobot, Robert, and Herwitz, George: J. ALLERGY **8**: 427, 1937.
5. Peshkin, M. M., and Fineman, A. H.: Am. J. Dis. Child. **37**: 39, 1929.
6. Levine, Philip, and Coca, A. F.: J. Immunol. **11**: 435, 1926.

DISCUSSION

DR. M. MURRAY PESHKIN, New York.—I am gratified to learn that the work on passive transfer reported by Dr. A. H. Fineman and myself in 1929 has been confirmed by Dr. Withers. We tested 18 children (scratch and intradermal technique) with 15 foods, including several biologic food groups. A total of 270 passive transfer tests with food substances were performed. In this discussion only our results with the intradermal method of testing were considered, since this technique was employed by Dr. Withers in his study.

Of the positive skin reactions obtained by the direct test in the children in our series, 31 per cent reacted by passive transfer. These figures strikingly compare with those reported by Dr. Withers. It was of interest to note that of the three-plus reactions obtained by direct test, 43 per cent reacted by passive transfer; of the two-plus reactions, 33 per cent; and of the one-plus reactions, 27 per cent responded by passive transfer. The plus-minus and negative reactions obtained by direct test were negative by passive transfer.

We had a small group of children who showed by direct test positive reactions to such foods as milk, chicken, beef, and lamb. These foods were proved etiologic factors of asthma, but on passive transfer negative reactions were obtained with all of these substances. We then concluded that the passive transfer method of testing, employed as a routine measure to determine etiologic sensitization in children, was unsatisfactory and impractical. Our findings confirm in essential details the excellent work of Dr. Withers.

DR. BRET RATNER, New York.—It is a pleasure to be in total agreement with Dr. Withers. We too found that individuals who were sensitive to more than one allergen might have an atopic reagin to one and not to another.

We also found, and I wonder whether you did, that repeated attempts to find the atopic reagin in the same patient resulted in finding it at certain times and not at others. This observation is significant, because it seems to me that the atopic reagin must be a humoral antibody which is present at certain times and not at others. Only at times when the antibodies are in the circulation will you find the atopic reagin present. I am, therefore, in total agreement with Dr. Peshkin's remarks, and I feel that the atopic reagin cannot be relied upon for diagnostic purposes

DR. GEORGE PINESS, Los Angeles.—I should like to ask Dr. Withers how he evaluates clinical food sensitivity. One hears a great deal about clinical food sensitivity. It would be most interesting to know what his postulates are for determining the degree of positiveness of these so-called clinical reactions.

We have felt, as Drs. Withers and Ratner as well as others, that biologically related foods, particularly when studied by Dale-Schultz methods, do not prove cross reactions or relationship, and that these foods have specific allergens common only to themselves. I am convinced that the botanical classification is of no real value from either a practical or an experimental standpoint.

DR. I. S. KAHN, San Antonio.—I should like to know if the essayist or any of the discussants have ever noticed any difference in the ability to secure positive skin tests in these food cases if the test is made at a time when the individual was off the food for a number of days or weeks, or has been intentionally fed that food for several days before the test has been done.

DR. WITHERS.—I will answer Dr. Piness's question first as to how clinical sensitivity is evaluated. In the first place, I felt that is common knowledge among allergists, that there is only one way definitely to establish allergy and that is by clinical trial, and by that I mean by precipitating or producing the original symptoms of which the patient complains by deliberately feeding the food to which we suspect or have proved that he is sensitive.

DR. PINESS.—How much time must intervene between the food and the reaction?

DR. WITHERS.—I think it is generally understood that the time that elapses between injection of food and production of symptoms is a variable factor, and it varies in different patients for the same food, and in the same patient for different foods; in fact, I know that is so because I have seen it happen that way many times.

In regard to Dr. Ratner's question of whether or not the reagins are constantly present in the blood stream, I have no way of knowing whether that is true or not. I have not worked with that idea in mind, but I do not believe that they do vary as the skin tests do, and, as I mentioned in the paper, it may be that we would have obtained more positive results if these patients had not eliminated foods to which they were sensitive for some time. I am not sure whether or not it has any effect directly on the skin test immediately, but I think that it does not.

DR. RATNER.—Not the skin test; just the antibody.

DR. WITHERS.—I am not in position to know. I have not worked that out, but I believe that the antibodies do vary from time to time.

Now, in regard to Dr. Kahn's question, when patients are off a food for a certain time, I think the antibodies are fixed in the skin and there is not such great variation in skin testing, but if foods are out of the diet for a long time, it may make some difference.

THE CHEMISTRY OF ALLERGENS*

I. Isolation of an Active Fraction From Cottonseed

Joseph R. Spies, Ph.D., Harry S. Bernton, M.D., and
Henry Stevens, Ph.D.
Washington, D. C.

INTRODUCTION

THE purpose of this investigation is the isolation and chemical characterization of the component or components of cottonseed which are capable of provoking allergic crises. This report of progress deals with procedures which have led to the isolation of a potent allergenic fraction from the water-soluble constituents of cottonseed embryo. In clinical studies, this fraction has exhibited a high degree of specificity. It induces skin reactions in high dilutions by direct tests and in passive transfer sites with satisfying uniformity. A procedure is described, which has been developed under the guidance of clinical tests, for preparing this fraction in sufficient quantity for chemical study. Results of preliminary chemical studies of the active fraction and some of its derivatives are presented.

SELECTION OF COTTONSEED REACTORS

During an interval of twenty months, all patients appearing at the Allergy Clinic of Providence Hospital have been tested for cottonseed sensitivity. In this survey, a cottonseed embryo extractive and commercial cottonseed allergens were used for cutaneous scratch tests. Patients who exhibited marked cutaneous sensitiveness to the commercial or to our own unfractionated cottonseed allergen preparations were subjected to further testing with various cottonseed proteins and other fractions of the seed. Inconsistent results obtained when testing with these fractions led to the presumption that cottonseed furnishes more than one skin reactive component and, further, that patients may manifest skin sensitivity to one or more than one of the active components. Patients who reacted positively to the whole cottonseed were retested repeatedly with serial dilutions of the available fractionated preparations to determine and compare thresholds of sensitivity. Four patients were finally selected on the basis of clinical evidence of allergy and the uniformity and similarity of their skin reactions. Continued clinical study of these four asthmatic patients guided the chemical procedures described in this report. Histories of these selected patients are reviewed.

*Contribution from Allergen Investigations, Bureau of Chemistry and Soils, U. S. Department of Agriculture, and the Allergy Clinic of Providence Hospital, Washington, D. C.

CASE REPORTS

CASE 1.—L. C., colored female, aged 49 years. Family history positive for allergy; has had perennial asthma all her life. Cutaneous tests positive for cottonseed, kapok, and tobacco. Serum shows the presence of reagins (allergic antibodies) for cottonseed.

CASE 2.—L. B., colored female, aged 48 years. Family history negative for allergy; has had perennial asthma, which is more severe in July and August, for twenty years. Cutaneous tests positive for cottonseed. Serum shows presence of reagins for cottonseed.

CASE 3.—C. L., colored male, aged 14 years. Family history positive for allergy; has had perennial asthma, which is most active from September to March, for thirteen and one-half years. Cutaneous sensitiveness to cottonseed and ragweed pollen. No reagins for cottonseed could be demonstrated in the serum of this patient.

CASE 4.—Q. N., colored male, aged 12 years. Family history positive for allergy. Generalized dermatitis of undetermined origin from two months to two years. Suffers from perennial asthma of eleven and one-half years' duration. No seasonal variation in symptoms. Cutaneous tests indicate multiple sensitiveness to epidermal proteins, pollens, etc., and cottonseed. Serum shows the presence of reagins for cottonseed.

MATERIAL USED

Material chosen for fractionation in this investigation was a choice quality of dehulled cottonseed, *Gossypium herbaceum*. The dehulled product is the embryo of the seed. It consists of whole and broken kernels, freed from endosperm, hull, and hull fiber or linters.

The initial step in the fractionation was extraction[1] of the cottonseed embryo with benzene (technical grade) at temperatures not exceeding 25° C. The word "cottonseed" is used subsequently to designate the ground residue remaining after removal of fat and other benzene-soluble components of the cottonseed embryo.

ISOLATION OF THE PROTEINS OF COTTONSEED

The methods described by Jones and Csonka[2] (modified in the preparation of the pentose protein fraction) were used in separating the known proteins. Essentially, this procedure comprised successive extractions of the cottonseed with aqueous sodium chloride to remove the salt-soluble proteins. The residue from the sodium chloride extractions was extracted with 0.1 N. sodium hydroxide. From the sodium chloride solutions were obtained the phosphoproteins, coagulated at 85° C., and the mixed alpha and beta globulins, coagulated at 100° C. From the salt solution remaining after separation of the heat-coagulable proteins, a pentose protein fraction was precipitated by ammonium sulfate at 0.8 saturation.* The native alpha globulin was precipitated by ammonium

*The term "pentose protein fraction" is used in referring to this preparation because later findings developed the fact that there was precipitated with the pentose protein an unidentified protein which was separated from the water-soluble constituents of the cottonseed.

sulfate. The native beta globulin was not isolated. The glutelin was precipitated by acidifying the alkaline extract. All fractions were dried in a vacuum desiccator over phosphorus pentoxide.

Skin tests with the separated proteins, in the solid state, resulted in strongly positive reactions, with no evidence of differentiation in activity. To determine whether the uniform skin reactivity of the different fractions was due to incomplete separation of the individual proteins, the several fractions were subjected to the following purification:

The coagulated phosphoprotein was stirred mechanically with 10 per cent sodium chloride solution and separated by centrifuging. This procedure, repeated four times with fresh portions of the salt solution, was followed by washing once with water. The solid fraction was dried in a vacuum desiccator over phosphorus pentoxide. In the same manner, the coagulated fraction of the mixed alpha and beta globulins was washed with water and dried. The pentose protein fraction was washed three

TABLE I

CUTANEOUS TESTS WITH PURIFIED PROTEIN FRACTIONS*

PROTEIN FRACTION	PATIENTS		
	L. C.	L. B.	Q. N.
Coagulated phosphoprotein	± 15 min.	± 15 min.	0 30 min.
Coagulated alpha and beta globulin	0 30 min.	± 15 min.	1+ 30 min.
Washed coagulated alpha globulin	± 15 min.	1+ 15 min.	
Pentose protein fraction	4+ 10 min.	4+ 10 min.	4+ 10 min.
Glutelin	± 30 min.	± 30 min.	

*These tests were made on the forearm. The solid protein was applied to a scratch and moistened with 0.1 N. sodium hydroxide. This procedure was used throughout for testing solid preparations.

Throughout this investigation, cutaneous tests were interpreted according to the following plan: Material to be tested was applied to a scratch 6 to 8 mm. in length, made by a single stroke with a needle. Dimensions refer to distance between boundaries of wheal perpendicular to the scratch.

0—Indistinguishable from control
±—Distinguishable from control
1+—Swelling and areola
2+—Wheal, 4-7 mm., with pseudopod formation and areola
3+—Wheal, 7-15 mm., with pseudopod formation and areola
4+—Wheal, 15-25 mm. (or larger), with pseudopod formation and areola

times in the same way with 0.8 saturated ammonium sulfate solution. The glutelin fraction was reprecipitated five times, after dissolving in several volumes of 0.1 N. sodium hydroxide, by bringing the pH of the solution to 4.4 with hydrochloric acid. The final fraction of glutelin was washed with water and dried in a vacuum over phosphorus pentoxide. The native alpha globulin was redissolved in 0.1 saturated ammonium sulfate solution and precipitated by increasing the concentration of the ammonium sulfate to 0.5 saturation. This procedure was repeated four times, and the final fraction was washed with water and dried as before.

Results obtained from repeated skin tests with purified protein fractions are summarized in Table I.

Purification of the individual proteins resulted finally in marked decrease of skin reactivity of all except the pentose protein fraction. It

was recognized that the decrease in activity of certain of the individual proteins might be due either to gradual removal of an active contaminant or to progressive alternation in the physiologic properties of the proteins. However, experience gained in clinical observations with intermediate fractionation products favored the hypothesis that the initial activity of the proteins was due to a contaminant which separated with them, and was removed more or less completely by the purification procedures. This hypothesis was supported by experiments which demonstrated the heat stability of a skin reactive factor and the observation that with sufficient washing, the proteins, excepting the pentose protein fraction, could be freed from significant activity.

Heat stability of the skin reactive component of the unfractionated cottonseed was determined by autoclaving for two hours, at 120 to 125° C., a 30 gm. portion of the cottonseed mixed to a paste with 100 c.c. of distilled water. This material, after autoclaving, was dried and tested by the same method previously used for the protein fractions. The activity of the cottonseed was not apparently diminished by this drastic heat treatment.

Decrease in activity, which resulted from coagulation and washing of the native alpha globulin, was apparently due to removal of an active contaminant rather than inactivation of the protein by heat coagulation. The effects of coagulation and washing were determined with the purified alpha globulin. The purified, solid, alpha globulin gave a 4+ reaction in ten minutes in cutaneous tests. A solution of this protein in dilute sodium chloride was heated for one-half hour at 100 to 104° C. The coagulated alpha globulin, tested in the solid state, was found to be still active. This coagulated globulin was washed thoroughly with water and dried. The washed and dried alpha globulin, separated by this procedure, was inactive when tested in the solid state. However, the salt solution from which the globulin had been separated by coagulation possessed undiminished activity. The fact that the activity of the native alpha globulin in solution disappeared at relatively low dilutions, furnished confimatory evidence of contamination.

Apparently a heat-stable, water-soluble component of cottonseed was responsible for the observed initial activity of the separated proteins. The undiminished activity of the washed pentose protein fraction was noted and tentatively attributed to contamination. This assumption was made because purification procedures comparable to those applied to the other proteins could not be used for the pentose protein fraction as a direct test of contamination.

Further study of the known proteins was abandoned, therefore, and attention directed to systematic fractionation of water-soluble constituents of cottonseed.

ALCOHOL FRACTIONATION OF WATER EXTRACT OF COTTONSEED

Two hundred grams of cottonseed was stirred mechanically with 1 liter of water for one-half hour. The residue was separated by centrifuging and subjected to a second extraction with 700 c.c. of water. The extracted solid residue was discarded. The water extracts were combined and divided into two equal volumes. One part was evaporated to a solid under reduced pressure at an outside bath temperature not exceeding 80° C. Final traces of water were removed from the residue by drying in a vacuum desiccator over phosphorus pentoxide. Twenty-six grams of a brown hygroscopic powder was obtained. The remaining portion of the water extract was heated to 100° C. for one hour. A voluminous brown coagulum separated and was removed by filtration through Celite.* The filtrate, evaporated and dried as before, yielded 23 gm. of a brown hygroscopic powder.

The dried residues from both the unheated and heated filtrates were separately subjected to the following fractionation:

Twenty-gram portions of the water-soluble residues were dissolved in 150 c.c. of water. Absolute alcohol was added to a final concentration of 25 per cent by volume. The precipitate, separated by centrifuging, was washed once with 25 per cent alcohol. This precipitate, the 25 per cent alcohol-insoluble fraction, was dried in a vacuum desiccator over phosphorus pentoxide. To the supernatant solution remaining after the separation of the first precipitate, absolute alcohol was added to bring the final concentration to 50 per cent by volume. A precipitate separated which was removed and washed once with 50 per cent alcohol. This residue, the 50 per cent alcohol-insoluble fraction, was dried in a vacuum desiccator as before. The supernatant solution remaining after separation of the 50 per cent alcohol-insoluble fraction was concentrated under reduced pressure to a volume of 100 c.c. To this solution, absolute alcohol was added to a final volume concentration of 75 per cent. A precipitate, the 75 per cent alcohol-insoluble fraction, was centrifuged, washed with 75 per cent alcohol, and dried as before. The supernatant solution was concentrated under reduced pressure to a volume of 15 c.c. To this solution, absolute alcohol was added to a final volume concentration of 90 per cent. A precipitate, the 90 per cent alcohol-insoluble fraction, was washed with 90 per cent alcohol and dried as before. The supernatant solution from the 90 per cent alcohol-insoluble fraction was concentrated under reduced pressure, and a solid fraction, the 90 per cent alcohol-soluble fraction, was obtained by complete removal of the solvent. This final solid fraction was dried in a vacuum as before.

The activity of the original mixture of water-soluble constituents and the products obtained from it by alcohol fractionation was compared by

*Analytical filter aid, supplied by Johns-Manville Co., Philadelphia, Pa.

determining the dilutions at which the different fractions induced skin reactions of approximately equivalent intensity. Results of these comparisons are summarized in Table II.

TABLE II

COMPARISON OF ACTIVITY OF FRACTIONS FROM HEATED WATER EXTRACT OF COTTONSEED*

FRACTION	MAXIMUM DILUTION FOR EQUIVALENT REACTIONS ON THIGH
Original, from heated (100° C.) water extract	$1:10^4$
25 per cent alcohol-insoluble fraction	$1:10^3$
50 per cent alcohol-insoluble fraction	$1:10^5$
75 per cent alcohol-insoluble fraction	$1:10^5$
90 per cent alcohol-insoluble fraction	$1:10^3$
90 per cent alcohol-soluble fraction	$1:10^2$

*Dilutions expressed in parts by weight of solid, dried in vacuum over phosphorus pentoxide, to parts of distilled water.

Further comparisons of the fractions from the water extract were obtained by observing the degree of skin response induced by $1:10^5$ dilutions of the fractionation products at the end of measured time intervals. Skin tests with all fractions at this dilution were conducted simultaneously. Results of these tests are summarized in Table III.

TABLE III

COMPARISON OF ACTIVITY OF FRACTIONS FROM HEATED AND UNHEATED WATER EXTRACTS OF COTTONSEED IN DILUTIONS OF $1:10^5$*

FRACTION	HEATED		UNHEATED	
	L. B.	L. C.	L. B.	L. C.
Original from water extract	1+	2+	1+	±
25 per cent insoluble	0	0	0	0
50 per cent insoluble	1+	4+	4+	4+
75 per cent insoluble	1+	4+	4+	4+
90 per cent insoluble	0	0	0	0
90 per cent soluble	0	0	0	0

*All reactions recorded in fifteen minutes. Cutaneous tests on thigh. Dilutions expressed in parts by weight of solid, dried in vacuum over phosphorus pentoxide, to parts of distilled water.

Comparative skin tests with products obtained by the alcohol fractionation of the water extract of cottonseed yielded definite evidence of separation and concentration of the skin reactive substance in the alcohol-insoluble precipitates. Maximum concentration of the active substance was obtained with the 50 per cent and 75 per cent alcohol-insoluble precipitates. These precipitates, which represented approximately one-twentieth of the water-soluble material of the cottonseed, appeared to be worthy of further study. The active substance in the fractions insoluble in alcohol was proved to be stable in all concentrations of alcohol, and was unaffected by boiling in 90 per cent alcohol. An advance in concentration of the active substance resulted from the observation that basic lead acetate precipitated a considerable quantity of unidentified, in-

herently inactive material, from aqueous solutions of the alcohol-insoluble fractions. On the basis of these observations, a method was developed for preparing the very active fraction, designated CS-1, in quantities sufficient for chemical examination.

PREPARATION OF FRACTION CS-1

One kilogram cottonseed was stirred one and one-half hours with 5 liters distilled water. The residue, separated by centrifuging, was stirred one and one-half hours with 3 liters of water. The extracted residue was separated and discarded. The combined aqueous extracts were boiled and stirred for five minutes and then cooled. Most of the coagulated material was separated by filtration through cheesecloth. The filtrate was concentrated to 1,200 to 1,500 c.c. by distillation under reduced pressure. This concentrated solution was stirred, while slowly adding alcohol to a final volume concentration of 75 per cent. The heavy, sticky, dark-colored precipitate formed a coagulum in a brown solution. This coagulum, separated from the supernatant solution by decantation, was dissolved in 1 liter of distilled water by stirring and warming. To this solution, alcohol was added to a final volume concentration of 25 per cent and, while stirring, there was added an excess of basic lead acetate solution (500 c.c. of 25 per cent alcohol containing 50 gm. of basic lead acetate). The precipitated lead salts were separated by centrifuging. Most of the colloidal lead salts which remained in suspension after centrifuging were not filtrable but could be removed by passing the solution through a Sharples supercentrifuge. Lead salts remaining in solution were precipitated by hydrogen sulfide and removed by filtration. Addition of about 70 ml. of the basic lead acetate solution before hydrogen sulfide precipitation seemed to aid in preventing the formation of colloidal lead sulfide. To the clear, almost colorless filtrate, alcohol was added to 75 per cent concentration. A white precipitate which formed was allowed to settle for twenty-four hours at –7° C. The supernatant solution, removed by decantation, was discarded, and the precipitate was recovered from the remaining solution by centrifuging. This precipitate was washed with 150 c.c. of cold 75 per cent alcohol and centrifuged. The washed precipitate (CS-1) was dried in a vacuum desiccator over phosphorus pentoxide. The yield was 0.8 to 0.9 per cent of an amorphous white solid.

The activity of the 75 per cent alcohol-insoluble fraction and the fraction CS-1 was compared by making simultaneous skin tests with equal dilutions of both fractions. Skin reactions in these tests were rated at the end of definite time intervals. Results of the comparative tests, which also serve as a measure of sensitivity thresholds of individual subjects, are presented in Table IV.

It is apparent that the activity of CS-1 is several times greater than that of the 75 per cent insoluble fraction.

TABLE IV

COMPARISON OF ACTIVITY OF 75 PER CENT ALCOHOL-INSOLUBLE FRACTION AND CS-1*

PATIENT	DILUTION									
	1:100,000		1:200,000		1:500,000		1:750,000		1:1,000,000	
	75 PER CENT INSOL.	FRAC. CS-1	75 PER CENT INSOL.	FRAC. CS-1	75 PER CENT INSOL.	FRAC. CS-1	75 PER CENT INSOL.	FRAC. CS-1	75 PER CENT INSOL.	FRAC. CS-1
L. B.			2+ 15 min.	4+ 15 min.	± 30 min.	1+ 30 min.	0 30 min.	1+ 30 min.	0 30 min.	0 30 min.
L. C.					3+ 15 min.	3+ 15 min.	0 30 min.	1+ 30 min.	± 15 min.	1+ 15 min.
C. L.	± 30 min.	2+ 30 min.	0 30 min.	3+ 30 min.	0 30 min.	0 30 min.				
Q. N.			0 30 min.	3+ 30 min.	0 30 min.	0 30 min.				

*Dilutions expressed in parts by weight of solid, dried in vacuum over phosphorus pentoxide, to parts of distilled water. Cutaneous tests on thigh.

PROPERTIES OF FRACTION CS-1

Several preparations of CS-1 have been obtained from the same and from different lots of cottonseed. These separate preparations of CS-1 were apparently uniform with respect to physiologic activity. The total nitrogen* content of the different preparations ranged from 14.7 to 15.8 per cent. CS-1 was insoluble in organic solvents but was readily soluble in water. Ninety per cent of the nitrogen was precipitated by phosphotungstic acid in dilute hydrochloric acid. Tested with the reagents usually used to identify proteins, CS-1 gave positive color reactions with all but the Hopkins-Cole reagent. With the biuret reagent, CS-1 gave a pink color. The sensitive Molisch test for carbohydrates was positive with CS-1, but no reduction was obtained with Benedict's qualitative test for reducing sugars. However, after hydrolyzing the CS-1 with boiling hydrochloric acid, a positive reaction was obtained with Benedict's reagent. The Bial test for pentose was positive. Results of the carbohydrate test indicated the presence of a polysaccharide which yielded pentose by acid hydrolysis.

TABLE V

EFFECT OF PRECIPITANTS ON CS-1 IN 1 PER CENT WATER SOLUTION

REAGENT	RESULT
Picric acid	Copious yellow precipitate
10 per cent trichloracetic acid	Copious white precipitate
Barium chloride	No precipitate
Barium hydroxide	No precipitate
Nitric acid	Yellow color
Hydrochloric acid	No change
Ammonium sulfate 0.7 saturated	Precipitate
Potassium mercuric iodide	Heavy white precipitate
Mercuric chloride	No precipitate
Mercuric acetate	No precipitate
Silver sulfate	No precipitate
Potassium ferrocyanide and acetic acid	Precipitate

The activity of CS-1 was not appreciably affected by high temperatures. One hundred milligrams of CS-1, dissolved in 50 c.c. of water, was autoclaved at 125 to 130° C. for one hour. A faint turbidity developed in the solution. The autoclaved material, diluted $1:10^5$, gave positive cutaneous tests.

Qualitative tests, with a variety of precipitants, are summarized in Table V.

TRICHLORACETIC ACID FRACTIONATION OF CS-1

Addition of an excess of trichloracetic acid to an aqueous solution of CS-1 resulted in a copious precipitate which, on centrifuging, was resolved into a slightly colored and a white precipitate. This observation suggested that fractional precipitation with trichloracetic acid might provide an additional means for further purification of an active constituent. Results of this experiment are summarized in Table VI.

*All nitrogen determinations were made by the Kjeldahl micromethod.

No appreciable fractionation could be obtained by precipitation with graded concentrations of trichloracetic acid. The three precipitates obtained were essentially uniform in total nitrogen content and in their activity when tested on sensitive patients.

TABLE VI

TRICHLORACETIC ACID (T.C.A.) FRACTIONATION OF 0.5 GM. CS-1 IN 25 C.C. WATER (T.C.A. Added in 20 Per Cent Solution)

FRACTION	CONC. OF T.C.A.	YIELD	FRACTION OF TOTAL	NITROGEN CONTENT	CLINICAL RESULTS CONCENTRATION OF SOLUTION $1:10^5$
	PER CENT	GRAMS	PER CENT	PER CENT	
1*	3.1	0.11	22.0	13.2	L.B. 3+ in 10 min. L.C. 4+ in 10 min. C.L. 0 in 30 min. C.L. 4+ $1:10^4$ in 15 min.
2†	5.5	0.19	38.0	12.8	—
3†	7.3	0.05	10.0	12.0	L.B. 3+ in 10 min. L.C. 4+ in 10 min. C.L. 0 in 30 min. C.L. 4+ $1:10^4$ in 15 min.

*Contains most of coloring matter.

†Fraction 2 was obtained from the supernatant liquid from fraction 1; fraction 3 from the supernatant liquid from fraction 2.

DIALYSIS OF CS-1

Duplicate 35 c.c. portions of a 2 per cent water solution of CS-1 were dialyzed against running water in collodion membranes, cast in 50 c.c. test tubes. The rate of dialysis was followed by periodic nitrogen analysis of the solution within the collodion sac. The results are shown in Table VII.

TABLE VII

DIALYSIS OF CS-1 AGAINST RUNNING WATER

TIME OF DIALYSIS	AVERAGE NITROGEN CONTENT OF SOLUTION WITHIN MEMBRANE	FRACTION OF TOTAL NITROGEN DIALYZED
Hours	*Mg./ml.*	*Per Cent*
0	2.85	
6	1.56	45.3
24	0.56	80.4
48	0.24	91.6
96	0.09	97.0
167	0.08	97.0

After one hundred and sixty-seven hours' dialysis, the solution within the sac contained 13 per cent of the original material, calculated on the basis of the residue obtained by addition of alcohol to 75 per cent, cooling to –7° C., and recovery of the precipitable solid. A 1 per cent solution of this residue gave no precipitate with 10 per cent trichloracetic acid or with saturated solution of picric acid, while an equal concentration of CS-1 gave copious precipitates with both these reagents. In eleven days,

significant decrease in activity of the undiluted inner solution was observed. After fourteen days' dialysis, the solid remaining in the sac was recovered by alcohol precipitation. It contained only 0.9 per cent nitrogen. Solutions diluted to $1:10^4$ of this solid gave negative skin tests. These observations indicated that CS-1 contained a protein and an inactive polysaccharide which were separable to a significant degree by dialysis.

PICRATE OF CS-1

A water solution of CS-1 reacted with a saturated water solution of picric acid with the formation of a copious yellow precipitate. Yields of

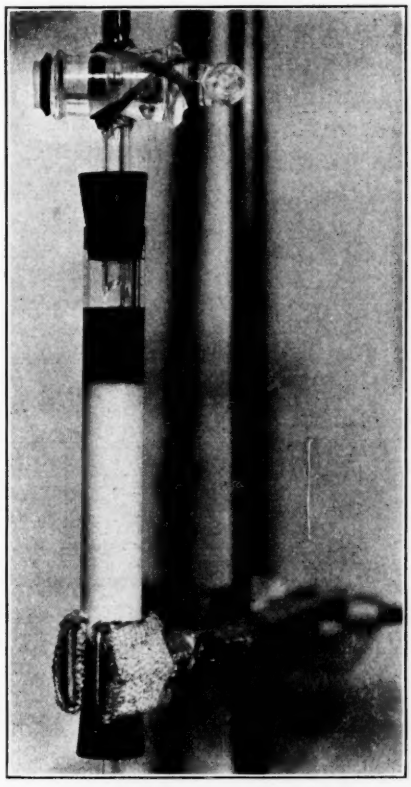


Fig. 1.—Layer of CS-1 picrate adsorbed on aluminum oxide.

the picrate represented 80 to 85 per cent of the weight of CS-1 in solution. This reaction proved to be of significant value in the purification and study of the chemical nature of the active factor in CS-1. Comparative skin tests of CS-1 and picrate of CS-1 at threshold dilutions have shown that they were not detectably different in activity. Skin tests with the filtrate obtained after precipitation of CS-1 picrate indicated that the precipitation of the active substance by the picric acid was practically complete. Evidence of an advance in purification of the active substance of CS-1 by picric acid precipitation was found in the fact that solutions

of the picrate, both before and after acid hydrolysis, gave negative tests with both the Benedict qualitative reagent for reducing sugar and the Bial reagent for pentose. These tests were controlled with solutions of known sugars to which picric acid had been added. These observations are in accord with the fact that picric acid did not precipitate the polysaccharide present in CS-1.

CHROMATOGRAPHIC STUDY OF CS-1 PICRATE

Selective adsorption is often employed to separate the components in mixtures of closely related chemical compounds. The term "chromatographic adsorption" has been applied to the procedure by which mixtures of colored substances in solution may be separated into layers while passing through a column of a suitable adsorbent. If the components of the mixture differ in their adsorption affinity toward the adsorbent, there will be a difference in rates of passage of the different components along the column when a solvent is passed through the adsorption column. Visual evidence of this separation of components becomes apparent in the formation of colored layers or bands along the adsorption column. Chromatographic adsorption may thus be used as a fairly delicate test of homogeneity. "A substance is homogeneous in a chromatographic sense when it is not resolvable in an adsorption column."[3]

TABLE VIII

COMPARISON OF ACTIVITY OF CS-1 PICRATE AND ELUTED CS-1 PICRATE SOLUTION 1:10^5*

PATIENT	CS-1 PICRATE	ELUTED CS-1 PICRATE
L. B.	3+ in 20 min.	3+ in 20 min.
L. C.	4+ in 10 min.	4+ in 10 min.
C. L.	3+ in 15 min.	3+ in 15 min.

*Control tests with solid picric acid were negative. Dilutions expressed in parts by weight of solid, dried in vacuum over phosphorus pentoxide, to parts of distilled water. Cutaneous tests on thigh.

The CS-1 was colorless, but the picrate of CS-1 was yellow. Both CS-1 and its picrate were apparently equal in skin reactivity and were adsorbed by activated aluminum oxide. These properties suggested chromatographic adsorption as a means of purification and for testing the homogeneity of the picrate.

The apparatus (Fig. 1) used in the chromatographic study was a glass tube containing a compact column of activated aluminum oxide* (Brockmann), with suitable fittings for passing solutions through the column under constant pressure. The dark band at the top of the column in Fig. 1 is a layer of adsorbed CS-1 picrate, which formed while a 0.2 per cent solution of CS-1 picrate in 50 per cent alcohol was being passed through the column. This experiment was repeated on a quantitative basis.

A solution containing 1.0 gm. of the CS-1 picrate in 500 c.c. of 50 per cent alcohol was passed through a 90 mm. column of aluminum oxide,

*Obtained from Merck & Co., Rahway, N. J.

contained in a tube 20 mm. in diameter. The picrate adsorbed by the aluminum oxide formed a sharply defined, intensely yellow layer at the top of the column. The solution collected after passing through the column was evaporated and from it 0.09 gm. of an inactive, yellow, crystalline material was obtained.

The layer of aluminum oxide containing the adsorbed picrate was removed from the column and eluted with 0.05 N. sodium hydroxide. The aluminum oxide was separated by centrifuging. The picrate was then precipitated from the alkaline solution by addition of an equal volume (excess) of picric acid solution. By this elution and reprecipitation, 0.90 gm. of picrate was recovered.

The eluted picrate possessed the same physiologic activity as the original picrate mixture, as shown in Table VIII.

DISCUSSION

The initial activity of the phosphoprotein, the mixed globulins, the alpha globulin, and the glutelin of cottonseed has been attributed to a contaminating substance which was in great measure removed in the process of purifying each protein. For the patients selected for this investigation, these proteins apparently possess no important degree of inherent activity.

Data assembled in the separation and study of the chemical and clinical properties of CS-1 and its derivatives have provided sufficient information to explain satisfactorily the observations recorded in the earlier examination of the proteins. The solubility of fraction CS-1 in water, saline, and alkaline solutions would account for the presence of this potent substance as a contaminant in all fractions of the proteins. Virtually complete removal of this contaminant from the proteins, excepting the pentose protein fraction, by the purification processes used, can be reconciled with the properties of CS-1 and the properties of the known proteins of cottonseed.

In the preparation of the pentose protein fraction, dialysis (employed by Jones and Csonka preliminary to precipitation) was omitted from our procedure. The pentose protein fraction referred to in this report contained, therefore, the pentose protein described by Jones and Csonka, and a considerable proportion of the fraction later separated and designated CS-1.

Attempts to diminish the activity of our pentose protein fraction by washing with 0.8 saturated ammonium sulfate were unsuccessful. The reason is apparent in view of the insolubility of the active fraction CS-1 in concentrated solutions of ammonium sulfate. The evidence available when the pentose protein fraction was used for skin tests warranted the assumption that its activity was due to ineffectiveness of purification for removing the suspected contaminant.

In their study of the proteins of cottonseed, Jones and Csonka recognized the fact that an important portion of the total nitrogen of their sodium chloride extracts was lost during dialysis of the heat-uncoagulable fraction. This diffusible fraction was precipitable by tungstic acid, but was not isolated nor further characterized. The diffusible protein postulated by Jones and Csonka is apparently represented in the fraction CS-1. The pentose protein described by these authors has not been studied sufficiently to establish its relationship with fraction CS-1.

Successive steps in the fractionation of the water extract of cottonseed were kept as simple and direct as possible to minimize the number of variables in the chemical procedures which might influence the activity of the skin reactive component. Products of each stage of the fractionation were separated, dried, and diluted on a weight basis for skin testing. This procedure permitted comparisons of activity and recognition of significant differences in potency, without dependence on assumptions concerning the chemical nature of the active component. Convincing evidence of progressive concentration of the active substance in the water extract was obtained from comparisons of the skin reactivity of the products separated in the alcohol fractionation. Finding that basic lead acetate precipitated a considerable quantity of inherently inactive material provided a modification which yielded a fraction, CS-1, having significantly greater potency than the 75 per cent alcohol-insoluble fraction. The method described for preparing CS-1 is an arbitrary procedure, developed from experience gained in conducting extractions and fractionations on a relatively large laboratory scale. Improvements in the method can doubtless be devised to increase the efficiency of the process. Losses of active material, inevitable in a procedure depending on fractional precipitations, have been recognized and judged unimportant.

The properties of CS-1 permit its classification as a proteose, according to the system adopted by the American Physiological Society and the American Society of Biological Chemists. Quantitative studies on the composition of CS-1 and its derivatives have not been completed. Recovery of the residue from a dialyzed solution of CS-1 provided the estimate that the nondiffusible carbohydrate comprises approximately 15 per cent of the whole fraction. More than three-fourths of CS-1 appears to be protein. Purification of the active portion of CS-1 by removal of carbohydrate has not been accompanied by demonstrable increase in activity of the resulting products. At present it appears that chemical and physical tests of homogeneity must replace biologic assays to determine differences in composition of fractions that range above 75 per cent in content of allergenic component.

When a solution of CS-1 picrate was passed through a column of activated aluminum oxide, nine-tenths of the original material in solution was adsorbed. An inactive, yellow, crystalline material, equivalent in amount to about one-tenth of the original CS-1 picrate, was recovered

from the solution that passed through the adsorption column. The adsorbed picrate, which may be recovered quantitatively from the aluminum oxide, was indistinguishable from CS-1 with respect to physiologic properties.

Evidence of approaching homogeneity of the eluted and reprecipitated CS-1 picrate, obtained from solubility and diffusion rate tests, is supported by results of preliminary chromatographic experiments. The picrate of CS-1 formed a uniform narrow band at the top of the aluminum oxide adsorption column. In an adsorption column of Celite, a wide but well-defined layer of adsorbed CS-1 picrate was moved down the entire length of a 50 cm. column without alteration in appearance. No adsorption was evident when a solution of CS-1 picrate in 50 per cent alcohol was passed through a column of silica gel. More conclusive chromatographic evidence of homogeneity of CS-1 picrate will require trials with several different combinations of adsorbents and developing solvents.

Several lines of evidence have led to the view that the activity and specificity of CS-1 depend on the protein alone and, further, that the carbohydrate and minor quantities of other inactive substances are extraneous to the allergenic properties of this fraction. The protein and the carbohydrate are separable by dialysis. The activity of the dialyzed solution of CS-1 diminished when most of the nitrogen had diffused out of a collodion sac which retained a large proportion of nondialyzable carbohydrate. Picric acid, a characterizing precipitant for proteoses, does not precipitate carbohydrates and does not interfere with the Benedict or Bial test for sugars. Picric acid formed a copious precipitate with an undialyzed 1 per cent solution of CS-1. After dialysis of CS-1, picric acid gave no precipitate with the recovered residue within the sac, made up to a 1 per cent solution. Picric acid precipitated practically all of the active substance from a solution of CS-1 in water. The picrate precipitate recovered from this reaction contained no detectable carbohydrate, but possessed the same physiologic properties as the original CS-1. These observations are pertinent to the role sometimes attributed to carbohydrates in allergic reactions. Available evidence justifies the conclusion that the activity of the protein in CS-1 was not perceptibly influenced by separating it from an associated carbohydrate.

Details of clinical studies of CS-1 and its derivatives will be presented in a separate report. However, some evidence of the allergenic properties of these fractions may be derived from a brief summary of clinical observations recorded during the progress of the fractionation studies.

Nonspecific skin reactions to CS-1 and CS-1 picrate have not been encountered in routine cutaneous tests with solutions of these preparations. Both CS-1 and CS-1 picrate gave negative results when used in the solid state for cutaneous tests on 32 allergic (cottonseed-negative) patients. Possibility of specific sensitiveness to picric acid or picrates has been recognized, but all control tests with picric acid have been negative.

Patients who have reacted positively to cutaneous tests with high dilutions of CS-1 and its derivatives have invariably reacted positively also to cottonseed and unfractionated saline extracts of cottonseed. Patients who react positively to cutaneous tests with "cottonseed allergens" of the type usually used to detect sensitiveness to this seed, do not invariably react positively to CS-1 and its derivatives.

Five patients, originally identified as cottonseed reactors on the basis of cutaneous tests with unfractionated cottonseed, were later found to react negatively to CS-1 and CS-1 picrate. These patients were studied extensively at the beginning of this investigation, but because of unexplainable irregularities in their response to skin tests with proteins and other cottonseed fractions, they were excluded from consideration in the final selection of suitable subjects for guidance of the chemical procedures. The serum of none of these patients contained detectable cottonseed reagin.

Reagins have been demonstrated in the serums of three of the four patients whose histories are cited in this report. All four of these patients have consistently shown positive reactions in cutaneous tests with unfractionated saline extracts of cottonseed and with high dilutions of CS-1 and CS-1 picrate. Sites passively sensitized with 0.1 c.c. of the sera of patients L.B., L.C., and Q.N., react positively to CS-1 and CS-1 picrate in dilutions ranging from $1:10^6$ to $1:10^8$, and to unfractionated extracts of cottonseed in lower dilutions. Attempts to demonstrate the presence of reagins for cottonseed or CS-1, or CS-1 picrate, in the serum of patient C.L. have been unsuccessful. However, this patient reacts positively to intracutaneous injection of 0.01 c.c. of CS-1 picrate diluted $1:10^8$.

Available evidence permits the classification of allergic cottonseed reactors into two types. Patients of Type I react positively to cutaneous tests with whole cottonseed or unfractionated extracts of cottonseed, and negatively to all dilutions of CS-1 and CS-1 picrate. Antibodies for cottonseed have not been demonstrated in the serums of these patients. The four allergic patients who have been studied most extensively in this investigation may be classified as cottonseed reactors of Type II. These patients react positively to unfractionated cottonseed and also to high dilutions of CS-1 and CS-1 picrate. Antibodies for cottonseed and for CS-1 and CS-1 picrate have been demonstrated in the serums of three of the four Type II patients. Constitutional reactions in the form of asthmatic seizures were provoked only in this latter group as a result of tests with cottonseed preparations. Two severe constitutional reactions resulted from attempts to obtain comparisons of the activity of the separate protein fractions. Precautions in testing the more highly purified fractions have prevented recurrence of these experiences. However, definite but mild symptoms of systemic reactions have been repeatedly observed in these patients when comparing the activity of several of the purified fractions in simultaneous tests.

Cutaneous sensitiveness to CS-1 and CS-1 picrate apparently signifies clinical sensitiveness to these fractions and to unfractionated cottonseed. Cutaneous sensitiveness only to unfractionated cottonseed extracts has not been correlated with other evidence of allergic sensitiveness to cottonseed. The successful guidance of the chemical fractionation of cottonseed depended on the early recognition and correct selection of a few patients whose cutaneous reactivity provided reliable evidence of allergic sensitiveness.

Cutaneous sensitiveness to the unfractionated cottonseed and CS-1, or CS-1 picrate, apparently does not signify clinical hypersensitiveness to refined cottonseed oil when used as an ingestant. The four patients, L.C., L.B., C.L., and Q.N., have shown no unfavorable clinical response from ingestion of cottonseed oil, U.S.P., when administered three times per week in doses ranging from 15 c.c. to 45 c.c. This phase of the clinical studies is to be continued with available patients of Type I and Type II, to determine their sensitiveness to products of the cottonseed usually encountered in the diet or environment.

SUMMARY

1. The known proteins of cottonseed embryo have been separated, and their capacity to induce positive cutaneous reactions has been compared.

2. A method is described for concentrating from the water extract of cottonseed embryo an allergenic fraction, CS-1, composed primarily of a protein and a polysaccharide.

3. The allergenic properties of the fraction CS-1 are attributed to the protein component.

4. Some chemical and clinical properties of CS-1 and a carbohydrate-free picrate of CS-1 are described.

5. Significance of differences in cutaneous sensitiveness to cottonseed and fractions of cottonseed, including CS-1 and CS-1 picrate, are discussed and interpreted.

6. The CS-1 picrate induces positive reactions by intracutaneous injection of 0.01 c.c. of a $1:10^8$ solution in passively sensitized sites.

The authors wish to acknowledge the valued services of Thomas H. Harris, B.S., for technical assistance in the chemical procedures and for the microanalytical determinations, and of Dorris C. Chambers, M.S., for assistance in the clinical studies.

REFERENCES

1. Drake, N. L., and Spies, J. R.: A Simple Large Capacity Extractor, Ind. Eng. Chem. An. Ed. **5**: 284, 1933.
2. Jones, D. B., and Csonka, F. A.: Proteins of the Cottonseed, J. Biol. Chem. **64**: 673, 1925.
3. Zechmeister, L., and Cholnoky, L. V.: Die Chromatographische Adsorptionsmethode, Berlin, 1937, Julius Springer, p. 5.

FURTHER STUDIES ON THE ALLERGENIC ACTIVITY OF PROTEIN AND NONPROTEIN NITROGEN FRACTIONS OF RAGWEED POLLEN EXTRACT*

ARTHUR STULL, PH.D., AND WILLIAM B. SHERMAN, M.D.
NEW YORK, N. Y.

THE protein nitrogen unit[1] for the standardization of pollen extracts for diagnosis and treatment of hay fever has been used in this clinic since 1932. This standardization was based upon the evidence[2] that the factor producing allergic reactions was associated with protein. A review of the literature and discussion of this subject have been published.[3] A previous publication[4] showed that purified protein of ragweed pollen neutralized ragweed sensitive serums in the same range as whole ragweed pollen extract when both were diluted to contain the same amount of protein.

Spain and Newell[5] confirmed the association of activity with the protein nitrogen and showed that phosphotungstic acid precipitated a small amount of nitrogen from ultrafiltrates of pollen extract. These filtrates on direct skin test were relatively inactive as compared with the residues.

The present paper is a further study of the relative activity of the protein and nonprotein nitrogen fractions of ragweed pollen. Whole ragweed pollen extract, a dialysate, a dialyzed extract, and purified pollen protein prepared by ammonium sulfate precipitation, were compared in neutralization of ragweed sensitive serum and in direct skin tests on ragweed sensitive patients. Also, a protein fraction precipitated from a different ragweed extract with absolute alcohol and ether at –10° C. was compared in neutralization of the same sensitive serum with fresh ragweed extract.

Preparation of Dialyzed Ragweed Extract and Purified Protein.—Forty grams of ether defatted low ragweed (*Ambrosia elatior*) pollen were extracted for twenty-four hours with 500 c.c. of alkaline saline (0.5 per cent NaCl and 0.27 per cent $NaHCO_3$). The pollen was filtered off, and 30 c.c. of the extract was put through a Seitz filter and designated L.R.1. Two hundred cubic centimeters of the same extract was dialyzed through a Visking membrane (Nojax) against 200 c.c. of alkaline saline for twenty-four hours, and the dialysate was run through a Seitz filter and designated L.R.2. The partially dialyzed extract was dialyzed for twenty-four hours longer against running water, 0.5 per cent NaCl and 0.27 per cent $NaHCO_3$ were added, and

*From the Department of Allergy, the Roosevelt Hospital, New York.

it was put through a Seitz filter and designated L.R.3. The remainder of the original extract (270 c.c.) was saturated with ammonium sulfate, the precipitated protein filtered off, redissolved in water, and reprecipitated three times by saturation with ammonium sulfate. The protein thus purified was freed of ammonium sulfate by dialysis against running water, 0.27 per cent $NaHCO_3$ and 0.5 per cent NaCl were added, and it was filtered (Seitz) and designated L.R.4. These extracts were analyzed for total nitrogen (T.N.) and protein nitrogen (P.N.),[3] the latter being determined by phosphotungstic acid precipitation with the following results:

		Mg. N per c.c.	
		T.N.	P.N.
L.R.1	Whole Extract	1.42	0.50
L.R.2	Dialysate	0.49	0.05
L.R.3	Dialyzed Extract	0.39	0.32
L.R.4	Precipitated Protein	0.52	0.48

Approximately one-third of the nitrogen of the whole extract (L.R.1) was precipitated as protein nitrogen. The dialysate (L.R.2) contained 0.49 mg. of nitrogen per cubic centimeter of which 0.05 mg. was precipitated by phosphotungstic acid. The dialyzed extract (L.R.3) contained only a small amount of nonprotein nitrogen. The total and protein nitrogen of the precipitated protein (L.R.4) agreed within the experimental error. These extracts, except L.R.2, which was used in concentrated form, were diluted in 0.85 per cent saline on a protein nitrogen basis (1 unit = 0.00001 mg. P.N.).

Comparative Neutralization of Sensitive Serum by Passive Transfer.—Neutralization of sensitive serum was done according to the quantitative technique used in previous experiments[6] at this clinic. Equal volumes of ragweed sensitive serum and the various ragweed preparations were mixed in vitro. Each mixture was injected into the skin of the back of a healthy (nonallergic) test subject, who gave negative intradermal tests to ragweed pollen extract containing 1000 units (0.01 mg. P.N.) per c.c. The sites were tested after forty-eight hours with 0.025 c.c. of ragweed extract, 1000 units per c.c. Table I is an example of one of these experiments.

The whole extract (L.R.1), the dialyzed extract (L.R.3), and the protein extract (L.R.4) in similar tests in 5 test subjects neutralized the same serum at approximately 100 units, although the total nitrogen of these 100 unit solutions varied from 0.0010 to 0.0028 mg. per c.c. The undiluted dialysate, L.R.2 (total N 0.49 mg. per c.c.), had no serum neutralizing activity, although approximately 10 per cent of its nitrogen, 0.05 mg. per c.c. (corresponding to 5000 P.N. units), was precipitated by phosphotungstic acid. This showed that a small amount of nitrogen precipitated from pollen extract by this reagent was inactive

in neutralization. In some experiments L.R.3 and L.R.4 showed slightly greater neutralizing activity than L.R.1. This might be attributed to the presence in the whole extract of the fraction of inactive nitrogen precipitated by phosphotungstic acid, but the differences were within the range of experimental error.

In direct intracutaneous tests on patients with ragweed hay fever, the extracts L.R.1, L.R.3, L.R.4 gave reactions of similar size when diluted to the same protein nitrogen content, while the dialysate, L.R.2, was comparatively inactive.

TABLE I

RAGWEED SENSITIVE SERUM (HR.)

NEUTRALIZATION

MIXTURE NUMBER	SERUM MIXED WITH	TOTAL NITROGEN MG. PER C.C.	PROTEIN NITROGEN MG. PER C.C.	UNITS PER C.C.	REACTION ON TEST WITH LOW RAGWEED 1000 UNITS PER C.C.
1	L.R.1	0.0014	0.0005	50	++
2	L.R.1	0.0028	0.0010	100	±
3	L.R.1	0.0056	0.0020	200	0
4	L.R.2	0.49	*		+++
5	L.R.3	0.00065	0.0005	50	+
6	L.R.3	0.0013	0.0010	100	±
7	L.R.3	0.0026	0.0020	200	0
8	L.R.4	0.0005	0.0005	50	±
9	L.R.4	0.0010	0.0010	100	±
10	L.R.4	0.0020	0.0020	200	0
11	Saline				+++

*L.R.2 contained 0.05 mg. N precipitated by phosphotungstic acid.

Precipitation of Ragweed Extract With Alcohol at –10° C.—A protein fraction precipitated by alcohol from a different whole ragweed extract by the method used by Horsfall and Goodner[7] for the extraction of serums, was also used to neutralize the same sensitive serum. Since this was done in an investigation of the possibility of preserving the activity of pollen preparations, the dried alcohol ether precipitated protein was dissolved at the end of ten months and compared in the neutralization of serum with a fresh extract and the original extract.

A low ragweed extract 36E, prepared Nov. 4, 1936, was divided, and one part was precipitated at that time by adding whole ragweed extract dropwise with shaking to absolute alcohol at –10° C. The precipitated protein was washed a second time with absolute alcohol and once with anhydrous ethyl ether at –10° C., and finally at room temperature with ether. The precipitate was dried in a desiccator, stoppered, and stored at 7° C. for ten months, when it was redissolved by adding sterile saline. The protein nitrogen content of this solution 36EA was 25,000 units per c.c. The original extract 36E, which had contained 40,000 units when prepared, was found after ten months on Sept. 7, 1937, to

contain 30,000 units per c.c. A fresh low ragweed extract, 37E, prepared Sept. 7, 1937, contained 45,000 units per c.c. These three preparations were diluted to contain the same amount of protein nitrogen and comparative neutralization of sensitive serum was carried out as previously described. Table II is representative of these experiments.

The fresh ragweed extract (37E) and the redissolved alcohol precipitated protein (36EA) neutralized serum (Hr.) at 100 to 150 units per c.c. The neutralization point was similar to that found with the rag-

TABLE II

RAGWEED SENSITIVE SERUM (HR.)

MIXTURE	SERUM MIXED WITH*	UNITS PER C.C.	REACTION ON TEST WITH LOW RAGWEED 1000 UNITS PER C.C.
1	L.R.36E Prepared Nov. 4, 1936	50	+++
2	" " " " "	100	+++
3	" " " " "	300	++
4	" " " " "	500	++
5	" " " " "	1000	+
6	L.R.36EA (Alcohol-Ether Ppt.)	50	+
7	" " " "	100	±
8	" " " "	150	±
9	" " " "	200	0
10	L.R.37E Prepared Sept. 7, 1937	50	±
11	" " " " "	100	±
12	" " " " "	150	0
13	" " " " "	200	0
14	Saline		++++

*Experiment performed Sept. 14, 1937.

weed preparations used in Table I. The redissolved precipitated protein 36EA was almost as active on a protein basis as fresh extract. The extract 36E, ten months old, did not neutralize the serum at a strength of 1000 units per c.c., showing that time not only decreased[3] the amount of nitrogen precipitated by phosphotungstic acid, but also lessened the neutralizing activity of the fraction so determined.

SUMMARY

1. Protein prepared either by dialysis of ragweed extract, ammonium sulfate precipitation, or precipitation by alcohol and ether at –10° C., neutralized the skin sensitizing antibody of ragweed sensitive serum at approximately the same strength as whole extract when all were diluted to contain the same amount of protein nitrogen. This is further evidence that the activity of ragweed pollen in producing allergic reactions is associated with protein.

2. The dialyzable nitrogen of ragweed pollen extract is shown to be inactive in neutralization of the skin sensitizing antibody. A small amount of this fraction is precipitated by phosphotungstic acid.

3. Dried protein precipitated from ragweed extract at –10° C. with alcohol and ether when redissolved after ten months showed almost the same activity in neutralization as fresh extract.

4. Ragweed extract at the end of ten months showed a loss of protein, and the remaining protein showed a marked loss of neutralizing capacity.

REFERENCES

1. Cooke, R. A., and Stull, A.: J. ALLERGY **4**: 87, 1933.
2. Stull, A., Cooke, R. A., and Chobot, R.: J. Biol. Chem. **92**: 569, 1931.
3. Stull, A., Cooke, R. A., and Tennant, J.: J. ALLERGY **4**: 455, 1933.
4. Cooke, R. A., Stull, A., Hebald, S., and Barnard, J. H.: J. ALLERGY **6**: 311, 1935.
5. Spain, W. C., and Newell, J.: J. ALLERGY **5**: 455, 1934.
6. Cooke, R. A., Barnard, J. H., Hebald, S., and Stull, A.: J. Exper. Med. **62**: 733, 1935.
7. Horsfall, F. L., and Goodner, K.: J. Exper. Med. **62**: 485, 1935.

ROENTGEN TREATMENT OF ASTHMA*

CHARLES K. MAYTUM, M.D., AND EUGENE T. LEDDY, M.D.
ROCHESTER, MINN.

THE use of roentgen rays in the treatment of asthma is by no means new, and most investigators have observed beneficial effects from such treatment. Various regions of the body, such as the spleen, adrenal glands, liver, thorax, long bones, and pituitary gland, have been irradiated, and there has been remarkably little difference in the results obtained.

In 1936, we reported the results obtained from irradiation of the mediastinum of 23 patients suffering from severe asthma. These patients were treated in the period from 1931 to 1934, inclusive. Five of them were markedly relieved for many months; 8 obtained marked relief for shorter periods. From January 1, 1935, to January 1, 1938, we treated by roentgen rays 215 patients who had asthma, and we wish to report now the results of this latter series. We realize that statistical studies of the results of the roentgen treatment of asthma are often of only questionable value and, at times, even misleading because of the multiple etiologic factors which are present in asthma. We admit also that almost any type of treatment—even a minor change in the usual medication or the trial of a new proprietary remedy—will relieve asthma in a certain number of cases. In the cases reported in this study roentgen therapy was employed only after specific or nonspecific therapy had failed to give relief, or in those cases in which a specific cause for the asthmatic attacks could not be found. Most of our patients fell in the latter group, although a few were known to be sensitive but had failed to obtain relief from the asthma by specific treatment. Some cases in which the patients had been given other treatment besides irradiation, which might have been responsible for the relief, are only mentioned in this report. No patients with mild asthma were treated with roentgen rays. About half of the patients were classed as having severe or very severe asthma, the rest as having moderately severe asthma. This, however, must be considered as a purely arbitrary classification.

The 215 patients in the present series who were treated by roentgen rays represent about 6 per cent of the total with asthma who were treated at the clinic during the period from January 1, 1935, to January 1, 1937. Twenty of the 215 cases could not be included in this report

*From the Division of Medicine and the Section on Roentgen Therapy, the Mayo Clinic, Rochester.

Read before the Association for the Study of Allergy, San Francisco, Calif., June 10, 11, 1938.

TABLE I

DATA ON PATIENTS WITH ASTHMA WHO OBTAINED MARKED RELIEF FROM ROENTGEN THERAPY

CASE	AGE YEARS	DURATION	SEVERITY OF ATTACKS*	DATE OF TREATMENT	RELIEF		REMARKS
					DEGREE	DURATION	
1	50	20 years	2-3, daily, 3 years	1/ 4/35			Sensitive to grass and ragweed
				2/ 6/35	Marked†	3 months	
				2/24/36	Marked	6 months	
2	38	7 years	3, constant, 2 years	1/26/35	Complete	6 months	
3	52	2 years	Moderate, bed 3 months	3/ 4/35	Complete	6 weeks+	Not seen again
4	62	1½ years	2+, moderate	4/26/35	Moderate‡	6 months	Slight wheezing each evening
				11/20/35	Marked	to date	
5	43	35 years	2+ winter, daily, 3 months	5/ 3/35	Almost complete		Mild winter attacks
6	34	4 years	Adrenalin daily, 4 years	7/16/35	Almost complete	2 months	Sensitive to aspirin
				12/ 2/36	Slight		Only adrenalin gave relief
				12/ 1/37	Almost complete	3 months	
				4/ 8/37	Almost complete	2 weeks	
				6/11/37	None, worse		
7	35	4 years	Moderate, 2 months	7/18/35	Complete	2 years+	Epilepsy, 1937
8	51	5 years	Moderate, daily, 6 months	8/16/35	Complete	To date	Still coughing
9	57	5 years	Moderate, almost daily	9/19/35	Complete	To date	Typhoid vaccine relieved for 5 weeks
10	33	3 years	2+, daily, 2 months	9/24/35	Almost complete	To date	Sensitive to pollen; 1 attack, 1936
11	61	33 years	3, fall and winter	10/31/35	Complete	3 months+	Sensitive to ragweed
12	64	10 years	3, constant, 2 years	9/26/35	Complete	2 months	A physician
				12/10/35	Complete	5 months	
13	43	8 months	3, constant, emphysema	1/31/36	Moderate	6 months	
				12/10/36	Moderate	6 months	

*Severity graded 1 to 4: 1 = mild; 2 = moderate; 3 = severe; 4 = very severe.
†Marked relief = 75 to 100 per cent.
‡Moderate relief = 50 to 75 per cent.

TABLE I—CONT'D

14	48	8 months	3, daily, bed 4 months	3/24/36 11/ 4/36	Almost complete Marked	2 months 6 months	Obese; hypertension
15	48	9 months	2-3	4/ 7/36 7/ 9/36 8/20/37	Complete Complete Complete	3 months 1 month To date	 Last treatment at home
16	51	10 years	4, emphysema	4/18/36	"Well"	6 months+	Last heard from September, 1936
17	47	2 years	2+, daily, 1 month	4/21/36 7/10/36	Almost complete to July Moderate to August	2 months 1 month	
18	46	20 years	Adrenalin daily 3 years	7/ 2/36	Almost complete	8 months	No adrenalin for 9 months
19	50	2 years	3, daily	7/ 4/36	Complete	To date	Nausea 2 weeks; asthma worse 2 weeks
20	48	5 years	2, daily	9/ 5/36 7/ 2/37	Marked Complete	6 months (Occasional attack) 3 months	
21	55	6 years	3	1/19/37	"Absolutely complete"	To date	
22	52	5 years	3, 2 months emphysema	3/ 9/37	Moderate	1 year	
23	54	20 years	Constant, 3 years emphysema	3/11/37 4/ 8/37 6/ 4/37 8/14/37 11/17/37	Occasional wheeze Almost complete Coronary occlusion on home trip Marked Moderate to marked	 7 weeks 2 months To date	 Asthma much better Caught cold; still wheezes
24	6	4 years	3-4, constant 2 years, oxygen for attacks	5/20/37	Complete	1 month	Sensitive to horse. One attack while riding, then better

TABLE I—CONT'D

CASE	AGE YEARS	DURATION	SEVERITY OF ATTACKS	DATE OF TREATMENT	RELIEF		REMARKS
					DEGREE	DURATION	
25	38	2 years	2	7/ 1/37 9/14/37	Almost complete Almost complete	2 months 2 months	Still coughs
26	50	18 years	3, daily, several years	7/ 1/37 4/ 7/37	Almost complete Almost complete	1 month 3 months then mild	First relief in 10 years
27	52	12 years	1½ years, adrenalin 3-5 times daily	7/22/37 11/29/37	Almost complete Almost complete	1 month 2 months	Attack after aspirin
28	37	9 years	3, daily, 3 months	9/17/37	Almost complete	To date	Sensitive to milk
29	71	19 years	3, daily, 4 months	9/23/37 11/10/37	Slight Gradual improvement	2 weeks To date	Occasional attack
30	47	12 years	1 month with hay fever	9/25/37 (pollen season)	Ended attack		Sensitive to pollen, aspirin
31	42	16 months	3, unable to work	10/13/37	Almost complete	1 month	Sensitive; then cough
32	59	1 year	3, 2-3 months, emphysema	10/15/37	Marked	2 months+	Still wheezed on exertion, no attacks
33	54		Moderate	10/23/37 11/27/37	Almost complete Almost complete	4 weeks 4 weeks	
34	57	17 years	2, emphysema daily	10/28/38	Complete	1 month 3 months mild	More treatment 4/20/38
35	45	4 months	3, hospital necessary	11/ 1/37	Complete	To date	Sensitive to iodides
36	24	6 years	?	11/ 3/37	Almost complete	1 month	Sensitive to aspirin. Asthma with acute cold
37	53	5 months	3, almost daily	12/16/37	Almost complete	1 month	
38	48	12 years	Moderate	11/ 3/35	Almost complete	To date	Mild asthma with colds

because treatment was incomplete or because the diagnosis of asthma was questionable, and another group of 34 cases is not reported because we were unable to follow the patients closely enough to determine whether or not relief was obtained. Of the remaining 161 patients, 38 (24 per cent) obtained more than 75 per cent relief, which lasted from one month to many months (Table I). An additional 23 patients (14 per cent) obtained as much relief but were not included in this group since other treatment given at about the same time may have been a factor in relieving the symptoms. Twenty-six (16 per cent) patients had from 50 to 75 per cent relief for periods of one month or longer. (Table II).

The remaining 74 patients (46 per cent) experienced less than 50 per cent relief, or more than 50 per cent relief for only short periods of

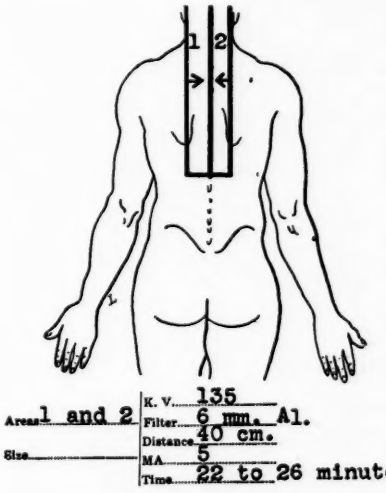


Fig. 1.—Irradiation of mediastinum through two paravertebral fields.

time, and the results are accordingly classed as failures. Two of the patients in this group were completely relieved of asthma but died within a month, one from coronary occlusion and the other from postoperative infection. Of this group for whom the results were classed as failure, 9 are dead, 4 having died from asthma, the rest from other causes. Four of the 74 patients in the group were addicted to morphine, and at least 13 had been under the care of recognized allergists prior to their registration at the clinic. Five patients felt that their asthma was definitely worse after treatment.

We have been unable to determine any criterion to judge which patients will be relieved by roentgen treatment and which will not. It is our impression that the more severe or more constant the asthmatic symptoms, the better is the chance for marked relief from roentgen therapy, and this impression would seem to be confirmed by Tables I and

TABLE II

DATA ON PATIENTS WITH ASTHMA WHO OBTAINED MODERATE RELIEF FROM ROENTGEN THERAPY

CASE	AGE YEARS	DURATION	SEVERITY OF ATTACKS	DATE OF TREATMENT	RELIEF		REMARKS
					DEGREE	DURATION	
1	59	4 years	Moderate, daily	1/31/35	Moderate	8 months	
2	61	4 years	Moderate, daily	3/ 9/36	Almost complete	2 months	Died at home
3	41	1 year	Moderate, winters	2/ 6/35	Moderate	2 months	
4	56	Several years	Moderate, daily	7/16/35 8/20/35	Moderate Marked	2 months	
5	7	6 years	Daily	8/24/35 9/17/35	Marked Moderate	1 month Several weeks	Recurred driving to clinic
6	63	3 months	Severe, 2-3 attacks daily	8/26/35	Marked	12 months+	Mild attacks, 1-2 times weekly
7	53	4 years	Moderate, daily, 3 months	9/19/35	Moderate	3 months+	Operation 10/23/35 without asthma
8	59	2 years	Moderate, daily	11/29/35	Moderate	4 months	
9	50	6 years	Daily for 5 years	12/ 7/35	Moderate	8-9 months	Gradual return
10	49	7 years	Daily, winter and spring	3/13/36 4/17/36	Moderate Marked	To date	Wheezing at times, no attacks
11	51	15 years	Daily, 6 years Severe, 6 months	3/19/36 4/14/36	Slight Marked	2 months+	Died, ruptured appendix
12	44	7 years	Moderate, daily 1 month	6/12/36	Moderate	18 months	Severe recurrence

TABLE II—CONT'D

13	55	14 months	Moderate, emphysema	6/19/36 7/22/36	Complete Moderate	3 weeks 2 weeks+	Flare-up during moving; no word since
14	48	20 years	Constant, severe for 5 years	7/17/36 8/27/36	Moderate Moderate	1 month 2 months	Lipiodol used
15	54	1 year	Moderate to severe, constant	7/24/36	Moderate	3 months	Cough persisted
16	54	5 years	Daily, constant, severe for 2 months	8/18/36 12/10/36 3/ 7/37	Moderate Moderate Moderate	3 months 2 months 4 months	1-2 attacks Only 2-3 attacks weekly. Last 2 treatments at home
17	45	12 years	Daily, severe	11/13/36	Moderate	1 month+	
18	43	2 years	Moderate, winter	9/17/36	Moderate	To date	Cough relieved. Sensitive to pollen
19	64	1 year	Moderate	3/ 5/37	Moderate	To date	
20	51	4 years	Moderate	4/28/37		2 months+	Last heard from in June
21	50	10 years	Moderate	5/21/37			Wheezes only in cold. Sensitive to pollen and foods
22	52	3 years	Moderate	6/28/37	Moderate	To date	No attacks since treatment
23	37	4 years	Daily, 3 years	8/24/37	Moderate	To date	Much treatment before without relief
24	66	1½ years	Moderate, daily	8/30/37	Moderate	3 months	Now only occasional attack
25	39	11 years	Severe	9/ 4/37	Moderate	3 months	2 short treatments at home later, no relief
26	49	2 years	Moderate	12/ 3/37	Moderate	To date	

III. The age of the patient and the duration of the asthma seem to make little difference. In most instances in which relief has been obtained once, subsequent treatment has also given relief, although in one case in this series and in one in the previous series failure resulted after the fourth or fifth treatment with roentgen rays. Most of the patients had only one roentgen treatment, and only a few had more than three treatments. Certain patients got less relief from the second treatment, and about the same number noticed more relief from it.

TECHNIQUE

In our first series of cases we irradiated the mediastinum through two paravertebral fields (Fig. 1). For the past two years we have been using an anterior and a posterior field (Fig. 2) over the mediastinum, as we

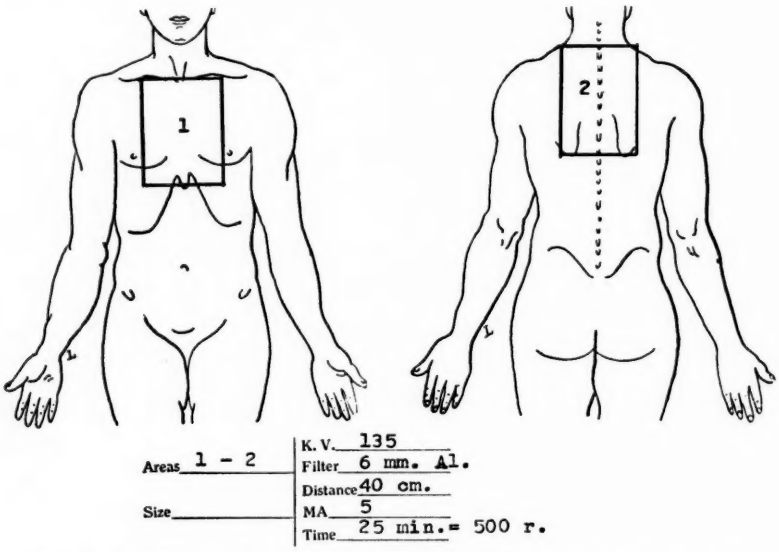


Fig. 2.—Irradiation of anterior and posterior fields over mediastinum.

thought that this technique might perhaps produce a better distribution of the rays in the thorax and, therefore, might improve our results. As a matter of fact, the latter supposition has not proved valid, and we now think that, if anything, anteroposterior cross fire of the thorax is, in general, a little harder on the patient. We have continued to give roentgen treatments on two consecutive days in the average case. If necessary, epinephrine is administered just before treatment and is occasionally given again during treatment.

In a small group of cases of asthma we have recently used one anterior and two posterior (paravertebral) fields, irradiation being at an angle of about 120 degrees, but the results in this group of cases are to date not conclusive. Only rarely have we treated the liver and spleen, alone or in conjunction with treatment of the mediastinum.

Approximately half the patients suffer no ill effects or at most only a mild malaise following treatment; about one-third have slight nausea for a few days but, only exceptionally, vomiting. We have seldom found indications for the use of pentobarbital sodium (nembutal). In an occasional case the cough and asthma may be increased slightly for one or two days. Other disagreeable effects are not often encountered, although 6 patients complained of thoracic pain and one complained of abdominal pain; one patient noticed a small amount of blood in the sputum immediately following treatment. There seemed to be no definite relationship between the amount of relief obtained and the reactions following treatment. Of the patients who were not relieved, 50 per cent experienced some disagreeable aftereffects from treatment; of those who obtained marked relief, 56 per cent experienced some aftereffects.

TABLE III

RESULTS OF ROENTGEN TREATMENT OF 161 PATIENTS WITH ASTHMA

	ENTIRE GROUP	OBTAINED MARKED RELIEF	OBTAINED MODERATE RELIEF	FAILURE
Patients	161	38	26	74
Average age, years	49	48.2	52	47
Average duration of asthma, years	8.6	9.2	5.5	11.2
Percentage with severe asthma	46	62	24	52
Percentage with moderately severe asthma	54	38	76	48

Some improvement in the asthma is usually noticed within a day or two, although the full effect is not obtained for from four to five days after roentgen treatment. In a few cases there is gradual improvement over a period of several weeks, but this is not common.

What is responsible for the beneficial effects of roentgen therapy in asthma is not definitely known. Desjardins' conclusion that the roentgen rays decrease the secretory power of the mucous glands in the trachea, liberate antibodies by destruction of leucocytes, and may have a stimulating effect on the production of eosinophiles, is a plausible explanation. The psychic effect of roentgen therapy must also be considered, although it seems as if the relief was of too long duration for this effect to be of any great importance. Relief may possibly be due to the analgesic effect of roentgen rays on the nervous system, in much the same way as relief from pain is obtained in certain types of neuralgic or neuritic pain.

With the doses of roentgen rays we have used, there is no danger of injuring the skin or thoracic structures, although improper dosage or too frequent treatments may do a great deal of harm. We believe that

with the dosage we have indicated (Figs. 1 and 2) there is no contraindication to repeating roentgen treatment several times at intervals of a month or more.

SUMMARY

The results of the roentgen treatment of 161 patients with moderately severe or severe asthma are reported. Thirty-eight patients (24 per cent) obtained marked relief; 26 (16 per cent) were moderately relieved for periods varying from one month to many months. An additional 23 patients (14 per cent) obtained marked relief, but other treatment given at about the same time may have been partially responsible for the relief apparently obtained from roentgen treatment. Seventy-four patients (46 per cent) obtained less than 50 per cent relief, and the results were classed as failure.

In most of the 161 cases in this series, either no specific cause for the asthmatic attacks had been discovered or the symptoms of asthma had persisted in spite of all treatment; in all cases the asthma was moderately severe or severe.

Roentgen therapy has not been used in treating patients known to be specifically hypersensitive, with the exception of a few for whom it was employed in an attempt to bring about earlier relief of symptoms.

Roentgen therapy is not a method of treatment to be used indiscriminately, as considerable harm may follow overdosage or too frequent treatment. We have noted no harmful effects to date, although it is to be admitted that 5 patients thought that their asthma was worse following roentgen therapy.

Even though at present we favor treatment through paravertebral fields, we do not advocate this method to the exclusion of all others. The beneficial effects from roentgen therapy are only temporary, and cures of asthma are not to be expected. We believe that the results we have obtained justify its use as an adjunct to the treatment of certain patients with severe asthma who have not been relieved by other measures.

DISCUSSION

Dr. Albert H. Rowe, Oakland, Calif.—I think Dr. Maytum will agree that a further word of caution about the too free use of roentgen therapy in bronchial asthma is wise. It is very important that the medical profession understand that such therapy must not supplant proper allergic diagnosis and therapy. It is becoming increasingly evident, as shown in my practice, that with an aggressive and persistent attitude toward the problem of the severe and chronic asthmatic, excellent or satisfactory results are usually obtained.

From the data presented, marked relief was obtained in 24 per cent of the 161 cases. As I could read the charts, however, only about 10 of these patients were relieved for longer than six months. The rest had relief lasting from two or three weeks to a month or two. Relief of such duration as Dr. Maytum stated was probably only temporary.

May we know how long these patients were thoroughly studied and adequately treated by recognized allergic methods before roentgen ray treatment was given? Necessarily, many patients who go to the clinic remain for only one to three weeks. Did they receive the prolonged necessary study and treatment which is absolutely required in the handling of such cases?

DR. MAYTUM.—In answer to Dr. Rowe's first question about the danger. I think we all know that x-ray treatment may be a harmful procedure. Any qualified roentgenologist, however, should know the dosage that the skin will tolerate and the interval at which it can be repeated. Also, treatment should be given only by such a qualified roentgenologist. The recommended dosage should not do harm if the intervals are a month or more apart and if treatment is not repeated too frequently. If only short periods of relief are obtained, treatment should not be repeated more than a few times. Every effort should be made to determine the etiologic factors responsible for the attack. The amount of relief obtained is short in many cases; in many of them, however, it extends over a period of months or years.

Regarding the length of observation: it is true that some of the patients were observed for too short a period to be certain of all of the factors which are responsible, but I think the same can be said of any case.

SOME OBSERVATIONS ON THE BLOOD EOSINOPHILE COUNT IN ASTHMATICS

H. B. HUNT, M.D., M.R.C.P., BIRMINGHAM, ENGLAND

THAT the blood eosinophile count in individual asthma patients is not static but often subject to wide variations cannot fail to escape the attention of anyone who has performed serial counts. Nor is it possible to ignore the fact that average counts for individuals may exhibit marked differences. Yet up to the present it has been found impossible to account for these divergences in a satisfactory manner.

In the account given below several different factors which may conceivably have affected the counts have been examined and the findings compared with those of other observers.

The investigations to be described were performed on patients attending the Asthma Clinic of the Birmingham General Hospital during the twelve months commencing October 1, 1936. For convenience the year was divided up into quarters. Each patient making regular attendances at the clinic had a blood film prepared during the first and subsequent quarters that he or she attended. As these investigations were conducted concurrently with blood sedimentation rate estimations, it was found convenient to prepare the films from fresh citrated venous blood.

After the films had been stained, a differential white cell count was made, 200 white cells being counted in each instance. A total of 103 asthmatics (43 males and 60 females) was investigated. However, it was only possible to perform serial counts over the four quarters of the year on 27 patients, and during three quarters on 9 patients.

In all, 267 differential white cell counts were performed. Values ranging from 0 to 19.5 per cent were encountered, although neither of these figures was common. When more than one count was performed, one of the most striking features was the differences displayed by the same individual at various times. Brief reference to Table I, where the findings in 36 cases of asthma examined over three to four quarters of the year have been summarized, will illustrate this fact. Twenty-nine, or 85 per cent, of these patients had at some time a count of 5 per cent or under, but 20 or about 55 per cent exhibited an eosinophilia of 10 per cent or over.

TABLE I

SUMMARY OF FINDINGS IN 36 ASTHMATICS UPON WHOM SERIAL EOSINOPHILE COUNTS WERE PERFORMED OVER 3-4 QUARTERS OF THE YEAR

CASE NO.	AGE	SEX	OTHER ALLERGIC SYMPTOMS	CHRONIC BRONCHITIS	EOSINOPHILE COUNTS (PERCENTAGE OF WHITE CELLS)				AVERAGE*
					OCT.-DEC.	JAN.-MAR.	APR.-JUNE	JULY-SEPT.	
5	60	M	–	B		2.5	5.0	5.0	4
19	64	F	–	B	–	4.0	3.5	4.0	4
77	35	F	R	B	3.0	4.0	7.0	3.5	4
100	36	F	HF	B	–	1.5	2.5	2.0	2
142	66	F	HF	B	3.5	4.5	11.5	–	7
192	47	F	HF	B	8.0	3.7	4.0	8.0	6
221	24	F	–	B	6.0	4.5	7.0	9.0	7
226	56	F	HF R	B	7.5	4.5	7.5	13.0	8
237	67	F	HF	B	0.0	1.0	1.5	5.0	3
311	40	F	HF	B	14.0	3.0	6.5	7.0	8
321	18	M	HF	B	11.5	5.5	2.0	11.0	8
341	34	F	R	B	7.0	10.0	6.5	7.0	8
379	40	F	HF	B	2.0	4.0	2.0	10.0	5
380	43	F	HF	B	–	5.5	8.5	10.0	6
429	53	M	–	B	11.0	1.5	2.5	5.0	5
432	50	M	–	B	4.5	4.5	10.5	11.0	8
433	29	F	–	B	6.0	9.0	8.0	13.0	9
447	63	M	HF	B	7.5	12.5	1.0	12.0	8
452	53	F	HF	B	16.0	14.0	14.0	19.0	16
456	22	F	–	B	2.0	9.0	5.5	7.0	6
472	19	F	–	B	3.5	0.5	2.5	10.0	4
603	13	M	–	B	9.5	9.0	8.5	2.0	7
604	5	F	HF R	B	3.5	3.0	9.0	1.5	4
107	62	F	HF	–	3.5	3.5	1.5	3.0	3
211	42	M	HF R	–	3.5	7.5	10.5	9.0	8
261	32	F	HF	–	7.0	7.0	4.0	10.0	7
382	43	F	HF	–	5.0	6.0	6.5	3.0	5
445	12	M	R	–	7.0	6.5	6.0	–	7
478	53	M	–	–	3.0	5.0	7.0	3.0	5
519	31	F	HF R	–	13.5	3.5	2.0	6.0	6
578	11	M	–	–	5.0	19.5	5.0	7.0	9
579	20	F	HF	–	9.5	4.5	4.0	11.0	7
580	14	M	HF	–	4.0	4.5	1.0	–	3
582	14	M	R	–	–	5.0	3.0	6.0	5
592	39	F	HF	–	16.0	5.5	10.0	6.0	9
598	29	F	–	–	5.0	4.5	0.5	16.0	7

*Calculated to the nearest whole number.
HF = hay fever; R = rhinorrhea; B = bronchitis.

The average count for the whole series of 103 patients was 5.7 per cent. The average figures of several different investigators have been tabulated for comparison in Table II.

TABLE II

COMPARISON OF EOSINOPHILE COUNTS BY DIFFERENT OBSERVERS

OBSERVER	NO. OF CASES	AVERAGE COUNT
Baagoe (1928)	52 children in hospital	6.6 per cent
	40 children ambulant	9.5 per cent
	30 adults	7.3 per cent
Brown (1927)	193	7.0 per cent
Bray (1937)	100 children	7.4 per cent
Rackemann and Colmes (1929)	150	5.5 per cent
Unger (1936)	207	5.5 per cent

Neither age nor sex appeared to exert any definite influence upon the count. The findings are set out below in Tables III and IV, and are in accord with those of Baagoe (1928) and Brown (1927).

TABLE III

AVERAGE EOSINOPHILE COUNTS ACCORDING TO AGE IN DECADES

AGE	NO. OF CASES	AVERAGE EOSINOPHILE COUNT
1-10 years	6	5.3 per cent
11-20 years	19	6.0 per cent
21-30 years	19	6.6 per cent
31-40 years	29	5.6 per cent
41-50 years	14	4.4 per cent
51-60 years	11	5.6 per cent
61-70 years	5	4.8 per cent

TABLE IV

COMPARISON OF EOSINOPHILE COUNTS BETWEEN MALES AND FEMALES

	MINIMUM-MAXIMUM COUNT	AVERAGE COUNT	NO. OF CASES WITH AVERAGE COUNT OVER 5%
Males (43)	0.5—19.5 per cent	5.9 per cent	24 = 55.5 per cent
Females (60)	0.0—19.0 per cent	5.5 per cent	28 = 46.6 per cent

The question as to whether the type of asthma affects the degree of eosinophilia will now be considered. On theoretical grounds it seems probable that the so-called "allergic" type of asthma or the "extrinsic" forms may present a different type of eosinophile count from that encountered where an infective element is present.

In the present series of cases when a history of chronic bronchitis was taken as an index of infection, there did not, on perusing the case records, appear to be any marked difference in the eosinophile counts between those with and those without this condition. Reference to Table I, which is fairly representative of the whole series of 103 patients, will make this point clear. It will be seen that high average and high individual counts occur alike among those with, and those without, chronic bronchitis.

Knott and Pearson (1935), studying the sputum of asthmatics, classified it into three types: (1) Containing eosinophile leucocytes with little or no evidence of infection, (2) containing eosinophiles with fair numbers of pus cells and bacteria, and (3) containing few or no eosinophiles with heavy infection. They found the average blood eosinophile count for each of the three types almost identical, i.e., cases with little or no infection had similar eosinophile counts to cases with a heavy infection.

Rackemann (1918) concluded from his investigation of 150 cases that the percentage of eosinophile leucocytes is increased in asthma and that the degree of this increase was not different in "intrinsic" or "extrinsic" forms. Similarly, Brown (1927) performed blood counts

on 193 asthmatics and found that cases exhibiting specific sensitivity to foreign proteins had counts which did not appreciably differ from those without this sensitivity. Cooke (1932) found that in cases of infective asthma, patients with positive skin tests exhibited an eosinophilia more frequently than those without. In reviewing 207 cases of bronchial asthma, Unger (1936) found the average percentage of eosinophiles in the blood almost identical in the "intrinsic" and "extrinsic" forms. These observations suggest that an infective element produces no definite effect upon the eosinophile count.

There is no general agreement as to what happens to the eosinophile count during the paroxysm. Although this problem has received attention since the end of last century by Van Noorden and others, only recent observations will be referred to, and only observations which specifically refer to counts taken during the attack in contradistinction to those taken about the time when symptoms were bad.

Rackemann (1918), in several instances, observed the eosinophile count during attacks and during the intervals when symptoms were absent, but no definite relationship between count and symptoms was obvious. Bezançon and Bernard (1930) believe that the number of eosinophiles in the blood is increased during the attack and quote some evidence from French literature in support of their statement. Gillespie (1930) considered a fall during the attack was usual. Adam (1931) believed that there was commonly a preparoxysmal rise which may or may not fall during the attack. Bray (1937) cites 5 of his own cases which showed a remarkable fall in the eosinophile count with the advent of symptoms. The usual explanation of such cases is that the fall in the circulating eosinophiles is due to their accumulation in the bronchial tissues during the asthmatic attack.

In Table V-A counts taken during the asthmatic paroxysm before adrenalin had been administered are compared with those performed during the intervals of freedom in the same individual. The number of patients examined is necessarily small, since the investigation was carried out in the out-patient department. It was consequently uncommon to encounter patients during severe asthmatic attacks, although, of course, some degree of wheezing was quite commonly present. The results of 7 similar observations by Rackemann (1918) have been appended (Table 5-B). It is obvious that in these cases symptoms and counts cannot be correlated.

At this point the work of van Leeuwen and van Nieherk (1928) may be mentioned. These observers investigated 203 allergic patients, most of whom were asthmatics. They found that no relationship could be established between the frequency and degree of symptoms and the eosinophile counts in patients who were removed from contact with allergens in the air or food, but who suffered from attacks. While noting that certain factors which cause a lowering of the eosinophile

TABLE V-A

EFFECT OF ASTHMATIC ATTACK UPON THE BLOOD EOSINOPHILE COUNT

CASE NO.	EOSINOPHILE COUNTS IN ATTACK (PER CENT)		EOSINOPHILE COUNTS IN INTERVAL (PER CENT)			
19	4.0		*3.5**	4.0		
100	2.0		1.5	*2.5*		
211	9.0		3.0	7.0	*9.0*	10.0
226	9.0	13.0	4.5	7.5	*7.5*	
433	9.0	13.0	6.0	*8.0*	9.0	
447	12.0		*1.0*	7.5	12.5	
611	12.5		3.0	*8.0*		
627	7.0		7.0	*10.5*		
634	8.5		*7.0*			
640	5.0		*7.0*			
641	5.0		*3.0*			
643	9.0		*7.0*			
649	16.0		*8.0*			
652	5.0		*11.0*	5.0		
661	9.0		–			
664	3.0		–			
382	3.0		*5.0*	5.0	6.0	6.5

*The interval count nearest in time to the attack is italicized.

TABLE V-B

EFFECT OF ASTHMATIC ATTACK UPON THE BLOOD EOSINOPHILE COUNT (RACKEMANN, 1918)

CASE NO.	EOSINOPHILE COUNTS IN ATTACK (PER CENT)	EOSINOPHILE COUNTS IN INTERVAL (PER CENT)		
	2.0	2.3		
	8.0	3.0	5.0	3.0
	3.6	7.3		
	14.0	11.3		
	11.3	5.3		
	7.0	8.0		
	6.0	2.0	6.0	5.0

count will also cause an improvement in the symptoms, e.g., starvation, pneumonia, or fixation abscess, they found that even in such cases, improvement was by no means always bound up with a fall in the eosinophile count. They concluded that although blood eosinophilia was to be regarded as an accompaniment of allergy, nevertheless the frequency and intensity of the symptoms bear no definite relationship to the eosinophile count.

Baagoe (1928) was similarly unable to establish any exact connection between symptoms and eosinophilia. Thus, he found that the number of eosinophiles in the blood may be increased after a series of attacks, or in the absence of attacks, or that it may be normal during periods of attacks. However, he considered that, as a rule, the count was highest after attacks and lowest in the intervals. He found that stay in hospital tended to cause a fall in the eosinophile count and an improvement in the symptoms.

A possible factor in the production of an eosinophilia in asthmatics is the injection of vaccines and other foreign protein, which are so commonly employed in the treatment of this condition. Eosinophilia has been produced by such injections both in animals (Biggart, 1932; Walker Hall, 1935; Campbell and co-workers, 1935) and in man (Spangler, 1925; Ling, 1925), although according to Sternberg (1928) and Peshkin and Messer (1935) specific protein, e.g., pollen vaccine, does not produce this effect.

In Table VI are set out the eosinophile counts before and after injections of vaccines, peptone, or other "foreign protein" in certain asthmatics in the present series. In just under half of the instances, an increase over pre-existing levels followed injections. However, in some cases, the increase was very small. Furthermore, reference to column I of the table shows that the count is not usually static but even in the absence of injections may show marked variations. Thus, it seems doubtful whether the injections produced any effect upon the eosinophile counts.

Spangler (1925), who recorded variations in the eosinophile count of asthmatics following nonspecific protein therapy (erotalin), found that the maximum rise in the count occurred, as a rule, in about two days and fell to its previous level in about seven days. If such transient alterations occurred in the present series, it is obvious that they would escape detection.

There appears to be some relationship between the blood and sputum eosinophilia. Brown (1927) compared the blood and sputum counts in 123 asthmatics, and obtained the following results:

EOSINOPHILE CELLS IN SPUTUM	AVERAGE BLOOD EOSINOPHILE COUNT
None	5.5 per cent
Few	6.5 per cent
Moderate	8.0 per cent
Large numbers	9.0 per cent

Knott, Oriel, and Witts (1930) confirmed this relationship. In their series of 34 asthmatics, 22 had eosinophiles in the sputum, and 12 did not; 12 of the former group and one of the latter showed a blood eosinophilia. The results of Brown reproduced above parallel the findings of Knott and Pearson (1935) that the degree of eosinophilia in allergic wheals was proportional to the number of these cells in the blood.

Edilman and Karpel (1912) claimed to have demonstrated in asthmatics a urinary eosinophilia in association with the attack. However, in stained films of centrifuged deposit of urine from 8 patients in this series observed during an attack, no evidence of an eosinophilia was seen.

A glance at Table I suggests the possibility of seasonal variations in the eosinophile counts. To render any such changes more apparent, these results have been rearranged in Table VII-A. When reference is

TABLE VI

EFFECT OF INJECTION OF FOREIGN PROTEIN UPON THE EOSINOPHILE COUNT IN 58 ASTHMATICS

THERAPY	CASE NO.	EOSINOPHILE COUNTS APART FROM TREATMENT* (PERCENTAGE)			EOSINOPHILE COUNTS DURING OR JUST AFTER TREATMENT (PERCENTAGE)	
Peptone (intravenous)	5	2.5	(5.0)		5.0	
	77	3.0	4.0	7.0	3.5	
	433	6.0	8.0	9.0	13.0	
	472	0.5	2.5	3.5	10.0	
	579	(4.0	4.5)	9.5	11.0	
	611	3.5			8.0	12.5
	634	7.0	8.5		1.0	
	639	9.0			13.0	
	640	5.0			7.0	
	641	5.0			3.0	
Vaccine	100	1.5	2.5		2.0	
	192	3.7	4.0	8.0	8.0	
	221	4.5	6.0		9.0	
	237		1.0	1.5	5.0	
	311	3.0	6.5	14.0	7.0	
	341	6.5	7.0	10.0	7.0	
	382	5.0	6.0	6.5	3.0	
	427	5.0			2.0	
	429	1.5	2.5	11.0	5.0	
	433	6.0			8.0	9.0
	452	14.0	(16.0)		19.0	
	456	2.0	5.5	9.0	7.0	
	478	3.0	5.0	7.0	3.0	
	578	5.0	5.0	19.0	7.0	
	598	0.5	4.5	5.0	16.0	
	603	8.5	9.0	9.5	2.0	
	604	3.0	3.5	9.0	1.5	
	607	3.5	4.0		3.0	
	608	2.0	8.0		15.0	
	609	5.5	8.5		9.0	
	619	5.0			8.0	
	626	2.0			10.0	
Pollen vaccine	107	3.5	3.5		1.5	
	211	3.5	7.5		10.5	
	226	4.5	7.5	(7.5)	9.0	
	321	5.5	11.0		2.0	
	376	2.0			0.0	
	592	10.0			6.0	
	599	2.0			8.0	
	627	10.5			7.0	
Mixed inhalant vaccine	107	(1.5)	3.5	3.5	3.0	
	211	3.5	7.5	(10.5)	9.0	
	226	4.5	7.5	(9.0)	13.0	
	321	(2.0)	5.5	11.0	11.0	
	627	7.0	10.5		7.0	
	647	7.0			9.0	
	649	16.0			8.0	
Bee Venom (intracutaneously)	5	5.0			2.5	
	19	4.0			4.0	
	142	3.4			11.0	
	226	4.5	7.5		7.5	
	432	4.5			4.5	10.5
	447	7.5			1.0	12.5
	452	16.0			14.0	
	540	12.0			9.0	
	559	2.5			3.0	6.5
	562	3.5			6.5	
	579	9.5			4.5	4.0

*See footnote on opposite page.

made to this table, a definite tendency for the eosinophile counts to fall during the winter and rise during the summer months will be noticed. Similarly, when the results from the general series of 103 patients are arranged in a like manner (Table VII-B), this same tendency is no less marked.

TABLE VII-A

SEASONAL VARIATIONS IN THE EOSINOPHILE COUNTS IN 36 ASTHMATICS OBSERVED OVER 3-4 QUARTERS OF THE YEAR

PERIOD	TOTAL NO. OF CASES	PERCENTAGE OF EOSINOPHILE COUNTS			AVERAGE COUNT (PER CENT)
		5 PER CENT OR UNDER	FROM 6-10 PER CENT*	OVER 10 PER CENT	
Oct.-Dec., 1936	31	48.3 (15)	32.2 (10)	19.3 (6)	6.9
Jan.-Mar., 1937	36	61.6 (22)	30.5 (11)	8.3 (3)	5.3
Apr.-June, 1937	36	50.0 (18)	38.8 (14)	11.1 (4)	6.2
July-Sept., 1937	33	33.3 (11)	42.4 (14)	24.2 (8)	7.1

TABLE VII-B

SEASONAL VARIATIONS IN THE EOSINOPHILE COUNTS OF 103 ASTHMATICS (GENERAL SERIES)

PERIOD	TOTAL NO. OF CASES	PERCENTAGE OF EOSINOPHILE COUNTS			AVERAGE COUNT (PER CENT)
		5 PER CENT OR UNDER	FROM 6-10 PER CENT*	OVER 10 PER CENT	
Oct.-Dec., 1936	50	52.0 (26)	32.0 (16)	16.0 (8)	6.2
Jan.-Mar., 1937	65	66.1 (43)	27.6 (18)	6.1 (4)	5.1
Apr.-June, 1937	87	55.1 (48)	33.3 (29)	11.6 (10)	5.7
July-Sept., 1937	65	30.7 (20)	47.7 (31)	21.5 (14)	7.7

*Counts between 5 per cent and 6 per cent included.
Numbers in parentheses by percentages = actual number of cases.

When considering these seasonal variations, three factors must be borne in mind, viz., (1) the influenza epidemic occurred during the winter; also at this time colds and febrile illness are common; (2) 49 of the 103 cases gave a history of hay fever, although in all of them symptoms did not persist; (3) practically all of the injections of "foreign protein" were given during the third and fourth quarters (summer months).

Febrile conditions in general, e.g., following intravenous T.A.B. vaccine (Cowie and Calhoun, 1919), when induced by physical means (Krusen, 1937), or pneumonia or fixation abscess (van Leeuwen and van Nieherk, 1928), and influenza in particular (Smorodintseff and co-workers, 1937), will cause a fall in the eosinophile count, and it is possible that the seasonal variations described above were influenced by such factors, since the lowest values occurred during the second quarter toward the end of the influenza epidemic and at a period when colds and respiratory tract infections were common.

*All counts were taken apart from the treatment indicated in column 1. The results in parentheses were obtained in the course of some other injections, e.g., in Case 5, treated by peptone, 5 per cent occurs in parentheses in the first column of percentages with 2.5 per cent without parentheses. This indicates that the figure 5 per cent was obtained apart from peptone treatment, but in the course of other injections (bee venom); also that 2.5 per cent was recorded apart from any other treatment.

It should be stressed, however, that active infection does not always depress the eosinophile count. Mention has already been made of the fact that in the present investigations, estimations of blood sedimentation rate were performed concurrently. Results showed that the sedimentation rate in asthma, whether of the infective type or otherwise, was normal, and that fast rates were good evidence of active infection. It was, therefore, interesting to note that of 22 patients exhibiting fast rates, 13 had eosinophile counts below 5 per cent, 6 counts of between 5 per cent and 10 per cent, while in 3 cases, the count exceeded 10 per cent. In each of the above instances the differential white cell count and the sedimentation rate estimation were performed on the same sample of blood. Such facts make it very difficult to assess the importance of infections in producing the comparatively low average eosinophile count encountered in the winter season.

In hay fever subjects, a rise in the eosinophile count during the season of symptoms has been noted by Sternberg (1928). Of the present series of 103 cases, about half (49) gave a history of pollen sensitivity, either past or present. Sternberg believed that the eosinophilia which occurred among the hay fever patients, was the manifestation of a shock reaction, and was comparable to the eosinophilia which is said to accompany anaphylaxis in animals.

Several factors make it difficult to believe that pollen sensitivity accounted for the seasonal eosinophilia in the cases under investigation. One case of uncomplicated pollen asthma examined during a severe asthmatic paroxysm showed a count of only 3 per cent. Also, some of the patients with a history of hay fever did not display the typical increase, and on the contrary, those without, sometimes did so (Table I). Furthermore, it seems strange to think that an eosinophilia should accompany hay fever symptoms and not asthmatic attacks when one considers that the degree of eosinophilia is higher in asthma than other allergic disease (Brown, 1927). In the light of what has been said already, neither vaccine nor other injections influences the changes in the eosinophile count. Thus no definite cause for these seasonal variations can be found. There may be some factor tending to increase the count which operates during the summer months or, on the contrary, a factor present during the winter tending to diminish the count, or a combination of factors may exist. It seems very probable that similar variations occur in counts of hay fever subjects. At the present moment it is impossible to say whether these seasonal changes are confined to allergic individuals.

SUMMARY

The eosinophile count in individual asthmatics is not static as a rule, but often subject to large fluctuations. The exact cause for these fluctuations is not usually ascertainable.

An eosinophilia is quite common in bronchial asthma, but when large numbers of counts are made, the average usually lies only a little over 5 per cent.

It is impossible to differentiate on the basis of the eosinophile count between "intrinsic" and "extrinsic" asthma or between infective and noninfective forms.

Neither age, sex, symptoms, nor the injection of vaccines and other "foreign protein," appears to have any definite influence upon the count.

Seasonal variations characterized by a tendency for high counts in the summer and low counts in the winter have been described, but no suitable explanation could be found to account for them.

I wish to express my thanks to Professor W. H. Wynn for the facilities which he has given me in carrying out these investigations. This work was undertaken during tenure of the Richard Fenwick Post-Graduate Scholarship.

REFERENCES

Baagoe, K.: Am. J. Dis. Child. **171:** 35, 1928.
Bezançon, F., and Bernard, E.: Ann. de méd. **27:** 204, 1930.
Biggart, J. H.: J. Path. & Bact. **35:** 799, 1932.
Bray, G. W.: Recent Advances in Allergy, London, 1937, P. Blakiston's Son & Co.
Brown, G. T.: J. Lab. & Clin. Med. **12:** 1145, 1927.
Cooke, R. A.: Am. J. M. Sc. **183:** 309, 1932.
Cowie, D. M., and Calhoun, G.: Arch. Int. Med. **23:** 69, 1919.
Edilman, A., and Karpel, L.: Deutsche. med. Wchnschr. **38:** 1271, 1912.
Gillespie, M.: Brit. M. J. **1:** 1139, 1930.
Knott, F. A., Oriel, G. H., and Witts, L. J.: Guy's Hosp. Rep. **80:** 421, 1930.
Knott, F. A., and Pearson, R. S. B.: Guy's Hosp. Rep.: **85:** 94, 1935.
Krusen, F. H.: Am. J. M. Sc. **193:** 470, 1937.
Van Leeuwen, W. S., and Van Nieherk: Ztschr. f. d. ges. exper. med. **63:** 393, 1928.
Ling, C. Y.: Arch. Int. Med. **35:** 598, 1925.
Rackemann, F.: Arch. Int. Med. **22:** 517, 1918.
Rackemann, F., and Colmes, A.: J. ALLERGY **1:** 2, 1929.
Smorodintseff, A. A., Toshinsky, M.D., Drobyshevskaya, A. I., and Osetroff, A. I.: Am. J. M. Sc. **194:** 159, 1937.
Spangler, R. H.: Arch. Int. Med. **36:** 779, 1925.
Sternberg, L.: Am. J. M. Sc. **71:** 82, 1928.
Unger, L.: J. ALLERGY **7:** 364, 1936.

THE ORAL ADMINISTRATION OF RAGWEED POLLEN

J. H. Black, M.D.
Dallas, Tex.

IN 1927[1] and 1928[2] we published reports upon the laboratory and clinical investigation of the use of ragweed pollen orally in the treatment of ragweed sensitive patients. In was found that a glycerin-saline extract of ragweed pollen could be used in considerable amounts without any unpleasant effect, except in approximately 5 per cent of the patients who had some gastrointestinal disturbance. Absorption from the alimentary tract could be shown by the finding of the active constituent of ragweed pollen in the urine, but that a great deal of it was not absorbed was demonstrated by the findings in the intestinal contents. The use of pollen extract orally in coseasonal treatment of ragweed-sensitive patients gave us results which we felt at that time were fairly satisfactory.

Oral treatment with pollen, if it is as satisfactory so far as results are concerned as the hypodermic method, has some very distinct advantages. It offers freedom from constitutional symptoms following administration. I have never seen a constitutional reaction unless one so interprets the gastrointestinal symptoms, which a small per cent of patients show; but these symptoms were never alarming and one need have no fear of violent reaction in using this method of treatment. The patient finds it quite pleasing in that it avoids the frequent visits to the physician's office and the injection of the hypodermic needle, both of which are considered somewhat of a nuisance. Further, it makes it unnecessary to start treatment weeks in advance of the onset of the season, since a protective level may be reached quickly without fear of untoward results.

Following the publication of the two articles mentioned, I continued the use of the method with gradually diminishing numbers of patients. On careful checking it was found that the number of patients who obtained definite relief by this method was distinctly lower than the number relieved by hypodermic therapy. After a few years I abandoned the method entirely except for an occasional patient who found it giving entirely satisfactory relief and continued its use in preference to any other method.

During the ragweed season in 1938, at the request of a pharmaceutical company and with the use of material which they kindly provided, I rechecked the matter using a group of 40 patients who visited the office within a week preceding the onset of the ragweed season or after the

season had become established. The initial dose of 500 units once daily was increased by 500 units each day until symptoms subsided, or until a dose of 4000 units was reached. With the larger doses 1000 units were taken at a time and as many doses used during the day as was necessary to get in the required amount. The pollen was taken preferably on an empty stomach and followed by a glass of water.

Two patients complained of nausea and abdominal distress and stopped the treatment on that account. No others showed any untoward symptoms at all. Results were classified as excellent, good, poor, and none. Four were classed as excellent, 12 as good, 6 as poor, and 18 obtained no improvement at all. In other words, 40 per cent got what might be classed as satisfactory results, which is distinctly lower than can be expected by proper hypodermic therapy.

While this is a small group on which to base any conclusions, it is a group of unselected patients who were having hay fever which could be definitely established as due entirely to ragweed pollen and the treatment was started either immediately before or very early in the season so that ample opportunity was provided for proper evaluation of results. The results obtained are quite comparable to those secured over a period of a few years after the publication of the original articles and corroborate the opinion which was formed after that experience, which led us to abandon the use of oral therapy as a substitute for the hypodermic method.

It should be said that some patients were completely relieved of their symptoms by oral therapy. The difficulty lies, not in giving a satisfactory measure of relief in the individual patient, but giving enough of them satisfactory relief. Those who were relieved got just as much relief as could possibly be given by hypodermic treatment; the number of them who had such relief, however, was much smaller.

A very interesting, possibly significant, and valuable observation was made in the course of this investigation. A young woman who had started her treatment hypodermically rather late in the summer was having such violent reactions from each injection that when the season began she had not reached anything near a protecting dose, because of the necessity of repeating doses. She was given pollen by mouth with the hope that it might give her some relief while I was trying to build her hypodermic dose higher. To my amazement, as soon as the treatment was started by mouth it was found that reactions from hypodermic injections stopped and I was able to push her injections up quite satisfactorily without any reaction of any consequence, either local or systemic. I then repeated this procedure with two other patients who were having the same difficulty, one of whom had been taking pollen treatment for five years and had never been able to get her treatment up to a satisfactory level because of severe reactions. In each of these two patients the

results were the same. As soon as oral treatment was started the hypodermic doses could be pushed up without further trouble. It would be unwise to draw definite conclusions from findings in three patients, but they are interesting at least and provoke some thought. The question at once arises whether the gradual introduction of a large dose of pollen from the intestinal tract into the circulating blood neutralizes so large a number of antibodies that the injected pollen finds so few available that it cannot give considerable reaction. Aside from the theoretical significance, it may prove to be very helpful in this type of patient, who is seen at not infrequent intervals in the practice of every one giving pollen therapy.

SUMMARY

Oral therapy with ragweed pollen gives perfectly satisfactory results in some patients and fair results in a larger group, but does not compare favorably with the results obtained by hypodermic treatment. In three patients it was found that the oral administration of pollen made it possible to increase the hypodermic treatment much more rapidly than could be done before pollen was administered by mouth.

Material used in this work was supplied by Sharpe & Dohme, Philadelphia, Pa.

REFERENCES

1. Black, J. H.: The Oral Administration of Pollen, J. Lab. & Clin. Med. **12**: 1156, 1927.
2. Idem: **13**: 709, 1928.

Special Reports

SKIN REACTIONS*

V. A Contour Gauge for Measurement of Height and Breadth of Allergic Wheals

Harold A. Abramson, M.D., and Manuel H. Gorin, Ph.D.,
New York, N. Y.

THE only objective characteristic used at present to measure quantitatively the reaction intensity of the allergic wheal itself is the area of the wheal. During the reading of these reactions it is customary to feel the apparent "depth" and turgor of the wheal with the finger tips. Even though the area of the wheal is of extreme importance in estimating the reaction to allergens administered by the scratch or intracutaneous method, the record of the area is not sufficiently significant in all whealing reactions. Since the area of the reaction is primarily restricted to the area stimulated in dermographism, *urticaria solare,* etc., this criterion cannot be used in these conditions. A simple method designed to measure and record permanently both wheal *height* and wheal *diameter* is presented here. This method not only broadens the field of study of allergic wheals by the attainment of fairly precise data, but also widens the scope of investigations of skin papules whether produced experimentally or occurring clinically. It has proved especially serviceable in the comparison of wheals produced by various agents, e.g., those produced by histamine and ragweed.

CONSTRUCTION OF THE CONTOUR GAUGE

The device in use at present is diagrammatically shown in Fig. 1. For its construction the following materials are required:

(1) Square pencil leads, measuring 3.0 cm. in length and weighing approximately 60 mg. each, with a base of about 1 sq. mm.; (2) two glass microscope slides; (3) sheet aluminum; (4) cement; (5) adhesive tape; (6) a broad rubber band. As indicated in Fig. 1, pencil leads are cemented in place to separate the glass slides just the proper distance. This permits the vertical leads to move freely in the vertical direction. The horizontal leads act as bearings for the T-shaped aluminum plunger which presses against the last uncemented vertical lead. A broad rubber band, not shown in Fig. 1, encircles the slides and aluminum plunger with a slight degree of tension. The tension in the rubber band must be sufficient to hold the square leads firmly in

*From the Medical Service of Dr. George Baehr and the Laboratories of the Mount Sinai Hospital, New York.

place, except when an actual contour is being taken. A small square of adhesive tape is fixed over the glass edges of the slides to protect the rubber band. A U-shaped shield is cemented to the sharp end of the aluminum plunger to serve the same purpose. If the leads do not move freely in their vertical chamber between the glass slides, they are easily pared down to a smaller size by rubbing them on paper.

OPERATION OF THE CONTOUR GAUGE

A flat area of the skin (in our experiments the anterior aspect of the forearm) is chosen and marked. A base line is obtained by gentle traction on the aluminum plunger, which releases the leads so that their full weight rests vertically on the surface of the skin. It is desirable to choose the base line as straight as possible. Since the weight of the leads is insufficient to distort the skin appreciably, their ends

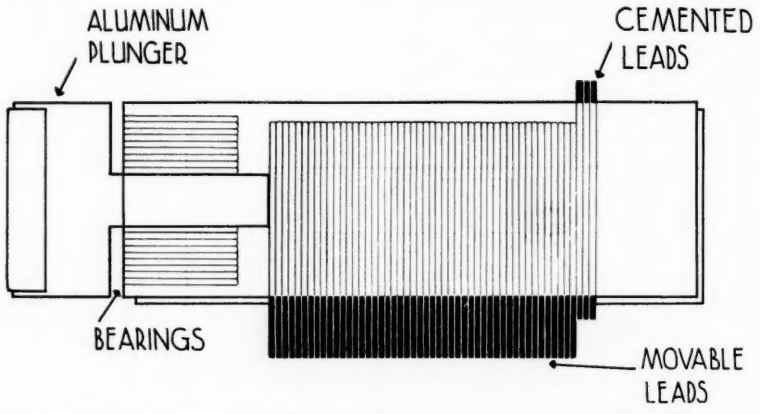


Fig. 1.—Diagram of the contour gauge. The rubber band which holds the aluminum plunger in place is omitted for clarity.

describe the true levels of the skin, about 1 mm. apart along the line of the gauge.

When the base line is recorded, the skin corresponding to the mid-portion of the base line is chosen to produce the wheal under investigation. In this way the rate of growth of wheals may be studied. If several gauges are available, measurements may be taken as often as desired.

RECORDING OF THE CONTOUR

Three methods have been developed to measure and record the height and breadth of the wheal.

1. The lower ends of the leads may be placed directly on cross-section paper and the wheal height estimated directly by observation.

2. (a) The lower edges of the vertical leads, which form the image of the skin elevation, may be supported by a glass microscope slide (both gauge and slide being kept horizontal) of suitable thickness, and

the outline formed by the edges transferred directly to a commercial type of transfer paper. (Magic copy paper was used.) This is accomplished by rubbing the surface of the paper in contact with the leads with a smooth cone-shaped rod, about the size and shape of some fountain pens. In our experiments the end of a fountain pen was employed.

(b) The outline formed by the leads may be transferred directly to any kind of paper by putting the paper under the leads, supported on a microscope slide, and gently running a fine pointed pencil, held vertically, along the ends of the leads.

3. A blue print transfer of the position of the leads may be made by illuminating a piece of blue print paper from above with the ends of the leads lying flat upon it. A small photo-flood lamp at a distance of 2 inches gives good prints with exposures of one minute.

Methods of Obtaining the Base Line.—(a) The base line is estimated and drawn. Then the maximum height of the wheal is the distance between the base line and the peak on the print.

(b) A base line may also be obtained by gently pushing a microscope slide blackened with India ink against the edges of the leads during exposure. An excellent cross section of the wheal is thus obtained. The blackened slide method can only be used with flat or convex contours.

Whenever a transfer method was employed, a pair of dividers was used to estimate the distance between the base line and the ends of the leads. The spread of the divider points was then measured directly on cross-section paper ruled in millimeters.

TABLE I

CALIBRATION OF CONTOUR GAUGE

GLASS	2 (a) MAGIC COPY PAPER TRANSFER	2 (b) PENCIL TRANSFER	3 (a) BLUE PRINT TRANSPER	3 (b) BLUE PRINT TRANSFER WITHOUT BASE LINE	MICROMETER
A	2.4	2.4	2.4	2.4	2.36
B	1.3	1.2	1.1	1.2	1.19
C	1.0	0.9	0.8	1.0	0.96
D	0.2	0.3	0.3	0.3	0.25

Calibration of the Gauge.—Four pieces of glass, varying in thickness from 0.3 to 2.4 mm., were used to estimate the limits of accuracy. In Table I are measurements obtained by the various methods described above for comparison with reference values found with a micrometer.

It is evident from Table I that there are no consistent errors involved in any of the methods, and that the maximum deviation from the most probable reading is about 0.2 mm. The average error, or roughly the probable error, is less than 0.1 mm.

GROWTH CURVES FOR HISTAMINE AND OTHER WHEALS MEASURED BY THE CONTOUR GAUGE

A detailed study of the rate of development and disappearance of a wheal can be accomplished by measuring the height of the wheal as it varies in time. It appears self-evident that the time at which the wheal

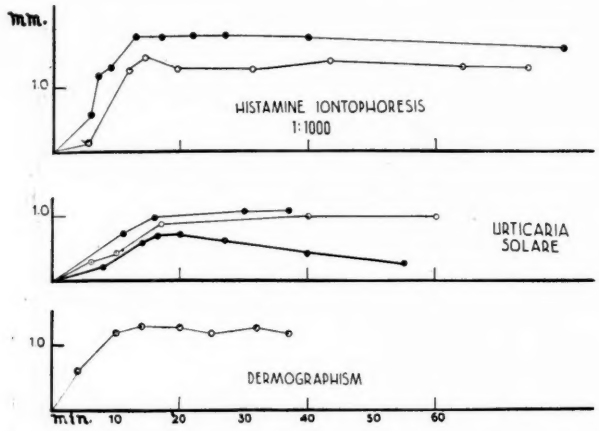
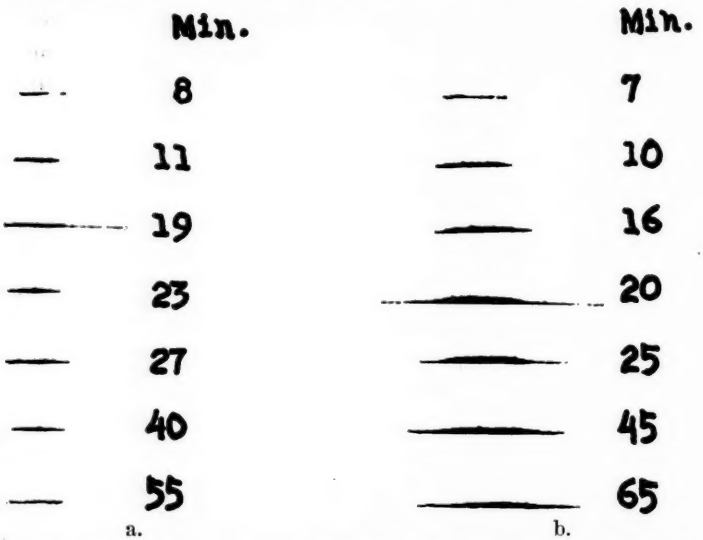


Fig. 2.—Various curves to illustrate the quantitative nature of the data obtainable by means of the contour gauge, the method described in the text. The height of the wheal and its persistence, of course, depend on the intensity of the stimulus, as well as the sensitiveness of the patient. These curves are purely illustrative and do not represent a systematic study of each type of stimulus.



a. b.

Fig. 3.—(a) Blue prints of wheal showing skin elevations as obtained by the contour gauge. The time in minutes indicates the rate of growth of the wheal. These wheals were produced by histamine iontophoresis. (b) Rate of growth and decline of wheal produced by ultraviolet light in a case of *urticaria solare*. Note the fairly rapid growth of the wheal and the more gradual diminution in height. See Fig. 2 for whealing produced in the same patient, which persisted at the same height for more than an hour with a stronger stimulus in the same patient.

has reached its maximum height is close to the time when the physiologic reaction of maximum intensity has been obtained, and for that reason such studies may prove to be of significance in the elucidation of the

whealing process. On the other hand, studying the spread of edema outside of the original boundaries of application is also of importance for the elucidation of material transport, of classification of reactions, of extent of reaction, etc. As a matter of fact, it has been noticed that the spreading of a wheal may continue long after the maximum height has been reached. Our method gives both height and spread of edema. Typical curves describing the growth rates of different wheals are presented in Fig. 2. The histamine (1:1000) was introduced by electrophoresis under carefully controlled conditions[1] of current density with electrodes of the same size. However, no attempt was made to further standardize the procedure. Factors, such as the maintenance of a state of rest in the subject, temperature of the room and of the solution applied, were not carefully controlled.

It is seen from Fig. 2 that the maximum height of the different wheals produced under our conditions is reached in from ten to twenty minutes, and then remains almost constant in some instances for more than an hour. Since plasma is being absorbed during this time (as evidenced by absorption of dyes[1]), these data indicate that although wheal growth practically ceases, a steady state exists between the volume of plasma entering the wheal from the blood capillaries and the plasma leaving the wheal through the lymphatics in the wheals under discussion.

In Fig. 3 are examples of cross sections of the growth of wheals obtained by blue print transfers described in method 3 (b). These cross sections represent the wheal growth in toto, including not only the white area of the wheal but also the adjoining edematous areas merging gradually with the unaffected skin.

SUMMARY

1. A method for the construction and operation of a simple contour gauge is described.

2. By means of the gauge the rate of growth of the height and cross section of allergic wheals may be measured and recorded.

3. Typical results are presented which indicate that wheals produced by histamine iontophoresis, by stroking, and by light usually reach a maximum height within twenty minutes. This maximum height may not decrease during the next forty minutes if the intensity of stimulation is sufficient.

4. The permanence of the wheal height and cross section, correlated with previous data on dye dilution and absorption during this period, indicates that a steady state is approximately maintained between the volume of plasma entering and leaving the wheal when the wheal height remains constant. With weaker stimuli the wheal height may decrease more rapidly.

REFERENCE

1. Abramson, H. A., and Engel, M.: Skin Reaction. II. The Effect of Allergic and Histamine Wheals on the Rate of Absorption of Dyes and Blood From the Human Cutis, J. Invest. Dermat. **1**: 65, 1938.

ASTHMA AND ALLERGIC RHINITIS DUE TO SENSITIZATION TO PHTHALIC ANHYDRIDE*†

Report of a Case

Richard A. Kern, M.D.
Philadelphia, Pa.

THE first case of asthma and allergic rhinitis found to be due to sensitivity to phthalic anhydride is here reported.

CASE REPORT

S. C. F., a chemist, aged 29, was first troubled in October, 1934, with stuffiness of the nose and a profuse watery nasal discharge. Soon after the onset there was also mild wheezing. Symptoms continued at intervals to December, 1934, when they practically cleared up. In March, 1936, the same symptoms, with perhaps a little more asthma, recurred and were present off and on until June, 1936. From late October, 1936, until June, 1937, he had mild recurrences lasting four or five days and at intervals of one to three weeks, but was free during the succeeding summer. On September 15, symptoms recurred, with greater severity than ever before, and at shorter intervals. He first consulted me on November 22, 1937. The patient's father had been asthmatic.

On further questioning, these significant facts were learned: His symptoms always began while he was at work. At first they began around 2 P.M. and grew worse as the afternoon progressed. More recently they have been starting at ten in the morning, becoming more severe as the day wore on. Relief was obtained by going to the dispensary of the industrial plant in which he was employed and there taking an inhalation of synephrin. Symptoms also would promptly clear up after he left the plant, nor would he ever have trouble during vacations away from the plant, irrespective of the season.

For seven years he has been employed as a chemist in a laboratory where paints are tested. There is no dust produced in the laboratory but considerable dust gets into the laboratory from other parts of the plant and from factories in the neighborhood. When he was asked if any particular dust seemed to bother him more than any other, he said that he had suspected phthalic anhydride.

Skin tests with an extensive list of substances gave a strongly positive reaction to crab, weak reactions to several other foods and to dog hair and horse hair. A scratch test with phthalic anhydride in crystalline form gave a violent local reaction with a wheal measuring over one inch in diameter and a zone of erythema of nearly three inches. A scratch test with a dilute alcoholic solution 1:1000 was also strongly positive. Neither the solution nor the actual crystals gave positive scratch reactions in normal controls.

*From the Allergy Section, Division of Medicine, University of Pennsylvania Hospital.

†Read before the Annual Meeting of the Society for the Study of Asthma and Allied Conditions, Atlantic City, N. J., April 30, 1938.

He was, therefore, advised to avoid contact with the material as much as possible. This he has been able to do by being transferred to another section of the plant. Since then his symptoms have practically abated.

Serum obtained from the patient was injected into passive transfer sites and these were then tested with phthalic anhydride 1:1000. Positive reactions were obtained, to our considerable surprise, since it is highly unusual to get a positive passive transfer test with a non-nitrogenous material.

Phthalic anhydride is the anhydride of benzene-ortho-dicarboxylic acid (phthalic acid). It has the formula $C_6H_4(CO)_2O$, and is a benzene ring substance. It occurs in rhombic prisms, having a melting point of 131.6° C. and a boiling point of 285° C. It is slightly soluble in hot water, soluble in alcohol, and particularly so in ether. It is made in large quantities by the catalytic oxidation of naphthalene vapor with air under carefully controlled conditions. (Naphthalene is usually sold under the common name of camphor balls or flakes.) Phthalic anhydride is the starting point for the manufacture of fluorescein and anthraquinone dyes. With glycerol it reacts to form a resin that is used in the paint industry.

The material is made in certain industrial plants in hugh quantities. An interview with the physician of one of these plants yielded the information that he had never observed respiratory symptoms due to the substance, but that contact dermatitis was a common occurrence among workers who handled it. They obtained relief only when they changed their occupation.

SUMMARY

1. The first case of asthma and allergic rhinitis found to be due to sensitivity to phthalic anhydride is reported.

2. An unusual feature of the case is the demonstration of circulating specific reagin to a substance of non-nitrogenous nature.

SULFUR DIOXIDE POISONING AS A CAUSE OF ASTHMA*

ALFRED ROMANOFF, M.D.
NEW YORK, N. Y.

MANY factors, such as cold, exercise, and overeating, have been recognized as nonspecific precipitating causes of bronchial asthma in individuals with a predisposed hereditary constitutional disposition. In all probability the inhalation of noxious gases, such as coal gas and sulfur dioxide gas, as well as the inhalation of gasoline vapors and fresh paint may be included in the same category of nonspecific precipitating causes.

Cooke[1] believed, on clinical grounds, that there may be a certain specificity in the inhalation of sulfur dioxide fumes, principally because this gas initiates attacks in relatively few asthmatic individuals, and in those who have been free from asthmatic attacks for a long time. However, there is no immunologic proof of the specificity of sulfur dioxide fumes in initiating attacks of bronchial asthma. It appears more likely, particularly in patients who have been exposed to a heavy concentration of sulfur dioxide fumes, that the primary effects are the result of an inflammatory, destructive lesion in the upper respiratory tract. The respiratory mucous membrane may be so altered that the bacteria already present or those inhaled multiply and gain access to underlying tissue to cause a suppurative bronchitis, as indicated in Case 1. Individuals who are constitutionally predisposed may respond to the products of the bacteria and develop a bacterial hypersensitivity, with a clinical symptom complex of bronchial asthma.

The inhalation of sulfur dioxide is very irritating to the upper respiratory tract. Even in low concentrations (0.001 per cent to 0.003 per cent)[2] it will cause sneezing, lacrimation, and a cough in most people. However, individuals who have been exposed to the sulfur dioxide fumes over a long period of time develop a certain degree of resistance, so that they can tolerate two or three times the above-mentioned concentration in the air, with little or no symptomatology.

Inhalation of sulfur dioxide gas has a deleterious effect on animals and human beings, and deaths have been recorded, following exposure of a few hours.[3] When sulfur dioxide is inhaled, contact with moisture transforms the gas to sulfurous acid which is rapidly oxidized to sul-

*From the Allergy Clinic, Mount Sinai Hospital.

furic acid. The gas is highly irritating, and in severe cases destructive lesions of the upper respiratory tract, such as bronchopneumonia and pulmonary edema, have occurred.

The effects of chronic exposure to sulfur dioxide have been studied. A group of 100 individuals, working in an electric refrigerator manufacturing plant, was investigated and compared with a healthy normal group of 100 people.[4] In the exposed group there was observed a diminution in the sense of taste and smell, an increase in the incidence of pharyngitis and tonsillitis, and increased fatigability and dyspnea on exertion.

Little cognizance of the role of sulfur dioxide as an exciting factor in attacks of bronchial asthma has been taken. No complete description of a case of asthma resulting from exposure to sulfur dioxide fumes had appeared in the literature until last year, when Dowling[5] described a case occurring in a repairman of electric refrigerators.

Within the past year we have studied the following three cases of bronchial asthma in men who had been working about electric refrigerators and who had been exposed to sulfur dioxide fumes.

CASE 1.—H. L., male, 32 years of age, was employed for ten years as a repairman of electric refrigerators. On a number of occasions he had been exposed to the fumes of sulfur dioxide from leaking refrigerators, and each time he had the usual reaction, consisting of fits of coughing, sneezing, and a running nose. Five days before admission to the hospital he was exposed to an unusually large concentration of leaking sulfur dioxide fumes, overcome with a severe attack of sneezing and coughing, and for the first time experienced breathlessness, with marked expiratory difficulty typical of bronchial asthma. He was seen by me at this time and referred to the Mount Sinai Hospital for further observation.

Physical examination disclosed a well-developed and well-nourished young adult male, with moderate cyanosis of the lips and fingernails. Respirations were labored and accompanied by audible wheezing. The chest was hyperresonant, and there was prolonged expiration with sibilant and sonorous râles. The remainder of the physical examination was entirely negative. Laboratory findings were negative.

While in the hospital he ran a rather stormy course, culminating in status asthmaticus. He was placed in an oxygen tent and helium was administered, but with only little improvement. He gradually improved, and began to respond to adrenalin injections, but frequent diurnal and nocturnal attacks of asthma persisted. These were accompanied by expectoration of large amounts of thick tenacious sputum which on a number of occasions was blood streaked. When he was somewhat improved, a bronchoscopic examination was performed. This revealed a large amount of cheesy secretion in both bronchi. Smears obtained from the exudate showed a great number of polymorphonuclear leucocytes, and occasional gram-negative and gram-positive diplococci. Search for acid-fast bacilli was without result. He remained in the hospital for the following two months with only slight improvement in the number of his attacks. X-ray of the chest on several occasions was always negative. Skin tests by the intradermal method were completely negative. At present, six months after the onset of his illness, he still has an occasional attack of asthma which responds well to adrenalin injections.

CASE 2.—I. G., male, 39 years of age, was employed as a repairman of electric refrigerators. He had never been previously ill. There was no family history or

personal history of allergic manifestations. He had been exposed to small amounts of sulfur dioxide fumes from leaking refrigerators for a number of months, and noticed the usual symptoms of running nose and burning sensation in the throat. One day after exposure to an unusually large amount of sulfur dioxide fumes from a leaking refrigerator, he experienced his first attack of difficulty in breathing. From that time on numerous typical attacks of bronchial asthma occurred. X-rays of his chest and sinuses were negative. Skin tests by the intradermal method revealed markedly positive reactions to chicken feathers and ragweed pollen, and moderately positive reactions to orris root, duck epithelium, dog epithelium, and rabbit epithelium.

He was observed for the entire following year, during which time he had frequent severe attacks of asthma which responded well to adrenalin injections. Since the patient observed no real improvement in his condition, he became discouraged and no longer sought medical advice.

CASE 3.—P. D., male, 37 years of age, was employed as a handy man in an apartment house. He had never been previously ill. There was no family history of allergy. Periodically, however, he had noticed a few urticarial wheals which he attributed to the eating of eggs. As part of his duties it was his job to keep the electric refrigerators in good repair and also to paint them with Duco enamel. He had frequently noticed some irritation of his eyes, running of his nose, coughing, and mild wheezing after exposure to leaking refrigerators. On one occasion after he had spent some time in an ill-ventilated cellar painting the boxes with Duco enamel, irritation of his nose and chest became especially noticeable. Despite these effects, he continued with his work. After some months, he again spent considerable time painting the refrigerators with Duco enamel. Following this, the previous mild wheezing became worse, and was accompanied by dizziness and weakness. He continued at his work for about ten days, but his attacks of respiratory difficulty became so severe that he had to enter the hospital.

On admission he was moderately cyanotic and dyspneic. Respirations were 24 a minute. He coughed spasmodically and brought up small amounts of thick tenacious sputum. There was normal pulmonary resonance throughout both lungs. Numerous sibilant and sonorous râles could be heard throughout both sides of the chest; prolonged labored respiration was noted. The remainder of the physical examination was completely negative. Laboratory findings were negative.

Skin tests by the intradermal method were completely negative, except for a slight reaction to egg white. Chest x-ray revealed no abnormalities in the lungs and a moderate enlargement of the left ventricle of the heart. While in the hospital, he continued to improve and was discharged twelve days after admission, still having moderate attacks of asthma. He was observed by his private physician for a few months, during which time he showed no further improvement. He became discouraged and discontinued his visits to the doctor.

This case is not as clear-cut as the other two, since there is the additional factor of Duco enamel, which is a complex mixture containing a number of acetates of alcohol, among them, amyl, propyl, and butyl. From the history of the case, it is apparent that the sulfur dioxide caused mild attacks of asthma, and the severe attacks were precipitated by the additional sensitivity to some element in the Duco enamel.

CONCLUSIONS

1. Three cases of prolonged bronchial asthma following exposure to sulfur dioxide fumes from leaking refrigerators are reported.

2. Sulfur dioxide refrigerants represent an industrial hazard, particularly for individuals with an allergic background.

3. An individual with a family history of allergy or manifestations of illness due to hypersensitivity, should not seek employment in an occupation in which he may be exposed to sulfur dioxide fumes.

REFERENCES

1. Cooke, Robert A.: Asthma in Children, Its Causes and Treatment, J. A. M. A. **102**: 664, 1934.
2. Sollmann, T.: Manual of Pharmacology, ed. 4, Philadelphia, 1932, W. B. Saunders Co., p. 192.
3. Hamilton, Alice: Industrial Poisons in the United States, New York, 1925, Macmillan Co., p. 324.
4. Kehoe, R. A., Machle, W. F., Kitzmiller, K., and LeBlanc, T. J.: On Effects of Prolonged Exposure to Sulphur Dioxide, J. Indust. Hyg. **14**: 159, 1932.
5. Dowling, Harry F.: Asthma Following Prolonged Exposure to Sulphur Dioxide, M. Ann. District of Columbia **6**: 299, 1937.

Society Proceedings

THE ASSOCIATION FOR THE STUDY OF ALLERGY

San Francisco, Calif., June 11, 1938

Further Studies on Respiratory Anaphylaxis: Experimental Asthma.
Bret Ratner, M.D., New York, N. Y. (Abstract.)

In 1927, Ratner and his co-workers devised a method by which they successfully sensitized and shocked animals solely by having them inhale a dry antigenic dust (horse dander) in a natural manner in a specially constructed chamber, yet observing the other criteria for true anaphylaxis. The symptom complex produced in the guinea pig was designated as "respiratory anaphylaxis," but these authors believed it bore sufficient analogy to the asthmatic syndrome in the human being to call it "experimental asthma." The method was devised to obviate the criticism that the anaphylactic state is an "injection illness," as Rössle called it, that is, it is produced in the experimental animal through the intravenous introduction of antigen, giving rise to a violent reaction process, and that it cannot therefore be compared with the allergic state in man. The procedure in Ratner's experiments is calculated to be more consonant with the conditions to which a human being may be exposed.

It is interesting that in a recent study Kallos and Pagel conclude that "the inhalation of finely sprayed homologous antigen produces in allergic guinea pigs attacks which clinically, roentgenologically, in their pharmacological response and even immunobiologically simulate human bronchial asthma in all respects."

Other investigators have likewise sought to sensitize and shock animals with the use of dry substances, but with little success. Inasmuch as Ratner and his co-workers have employed antigenic dusts fine enough to pass a 200-mesh sieve, they suggest that previous difficulties may have been due to the fact that the antigenic substances were not in fine powder form.

In subsequent studies these authors have shown that the fetus may be either actively or passively sensitized in utero, by having the pregnant female inhale the dry antigenic dust; that sensitization may be accomplished with an antigen other than horse dander, e. g., castor bean dust; that a guinea pig sensitized by having it inhale horse dander dust may become sensitive to the homologous horse serum; and that the administration of epinephrine successfully relieves the asthmatic symptoms in the animal.

Continuing their studies on experimental asthma in the guinea pig, Ratner and his co-workers in the present report show that the amount of exposure to the inhaled dust is another controlling factor in the establishment of the condition in the animal. When exposures reach a certain optimum point, the majority of animals become sensitized.

They have also demonstrated that by repeated short exposures asthmatic symptoms are produced in animals as successfully as after fewer, longer exposures. Animals sensitized solely through inhalation did not develop a state of antianaphylaxis after repeated shock exposures, as is commonly observed in animals which receive repeated parenteral injections. Practically each time that they were exposed they manifested asthmatic symptoms. This condition might be likened to status asthmaticus. However, on some days certain animals appeared to be nonreactive, but such periods were temporary and they manifested reactions on subsequent exposures; for example, one animal was brought into contact with the dust 43 times but developed only eight attacks of moderate respiratory distress. This brings the correlation with human asthma even closer.

Another question which engaged their attention was whether sensitization in animals repeatedly exposed in this manner to a dry antigenic dust is limited to the respiratory tract alone, or whether a remote organ, such as the uterus, also becomes sensitized. They devised a special technique to investigate this problem. They came to no conclusive answer, but hazard the suggestion that sensitization so induced may at first be limited to a local organ, and after continued exposure of the animal the sensitization may become more widespread and involve other organs.

One striking point that these experiments demonstrate is that animals vary greatly in their capacity to become sensitized. It has been assumed that in the experimental animal sensitization may be established with ease and regularity, whereas in man the disposition to become sensitized depends on genetic factors. Yet, these studies make it evident that certain animals are highly susceptible and become sensitized after small contacts, while other animals remain resistant when they have been exposed to repeated contacts which sensitize the majority of animals. These authors conclude, therefore, that when an environmental situation is reproduced in the animal which simulates more closely an environmental condition in man, than did the original anaphylaxis experiment, individual differences in susceptibility appear in the guinea pig just as they do in the human subject.

The authors are of the opinion that the method devised opens up wide possibilities for detailed investigations into the many phases of the problem of allergy resulting from the inhalation of antigenic dust. It may lead to a far more accurate modus operandi for evaluating therapeutic and preventive measures designed for application in the human allergic suffering from inhalant bronchial asthma or pollinosis.

DISCUSSION

DR. HARRY L. ALEXANDER, St. Louis.—Dr. Ratner is the first to demonstrate that one may sensitize guinea pigs by dry inhalants and one may shock guinea pigs so sensitized by the same dry inhalants. Before his studies it had been shown that guinea pigs could be shocked by liquid inhalants.

"Respiratory Anaphylaxis" is the title under which Dr. Ratner's earlier work appeared, and as such I think it is excellent. When the title now becomes changed to "Experimental Asthma," I feel there will be quarrel on many sides; in other words, bronchospasm in the guinea pig is now considered analogous to human asthma. I do not think there need be any question about it if asthma merely be wheezing. According to this conception, if one uses histamine in certain animals and causes bronchial spasm, it would be asthma because there is wheezing. If, however, asthma be what we consider it is in the human being, with all the attendant conditions of heredity, chronicity, etc., I think one will have to strain a good deal in order to reconcile them with mere bronchospasm in the guinea pig.

In man there is still debate as to what is the essential lesion in asthma. I think there is more and more feeling and evidence that it is mucous secretion that causes bronchial obstruction. Bronchospasm probably occurs also, but whereas some years ago it was thought that bronchospasm was the sole lesion, there is more and more evidence accumulating that the obstruction of the bronchi in human asthma is due to mucus. To my knowledge there are no prominent mucous glands in the bronchi of guinea pigs.

Secondly, although Dr. Ratner did not mention it, the antibody in man is the atopic reagin, and in the guinea pig the precipitins are identified with anaphylaxis. There is an indication that perhaps these are all colloidal expressions of the same antibody, but certainly that is not generally accepted as yet, and Dr. Ratner in his presentation must infer that all these antibodies are one and the same thing. That may be, but, there again, I think there are those who will quarrel with him. Therefore it might be safer, perhaps, if Dr. Ratner presented this work as respiratory anaphylaxis, which his experiments so clearly indicate, rather than to interpret them as true asthmas.

I do not take a positive stand on this controversial matter, but I think the question should be raised.

DR. HARRY L. HUBER, Chicago.—Did you keep the guinea pigs that were resistant to sensitization in favorable physical surroundings except for the exposure to the sensitizing antigen? Could you sensitize these same pigs by putting them in an unfavorable, heated or chilled, environment? In man is it not possible to have the protective mechanism altered sufficiently by chilling, fatigue, infection, etc., to set off the initial stage of sensitization?

DR. RATNER.—I will first answer Dr. Huber's question. Our animals were kept in a very well-regulated laboratory where there were proper heating facilities; as a matter of fact, any animal that was at all ill was immediately discarded. They were not used in any of these experiments. Several hundred animals were discarded.

Dr. Alexander raises some very pertinent questions, and I think that we are all familiar with them. It is all right for Dr. Alexander to like the term "respiratory anaphylaxis." I thought I liked it about ten years ago, and I still think that it is a very good term. I think calling asthma "respiratory anaphylaxis" is proper. The French use it exclusively. But I feel that we now have adequate justification for the use of the term "experimental asthma" in the guinea pig.

Dr. Sewall had no hesitancy in calling his studies in guinea pigs with the inhalation of liquid antigens "experimental asthma." Meltzer had no hesitancy in correlating guinea pig anaphylaxis and human asthma. Kallos has no hesitancy in calling his work experimental studies in bronchial asthma. Dr. Alexander wants me to fit in with a classification with which I am not in agreement. We are progressing in our understanding of the asthma problem. This work in the guinea pig, with the inhalation of dry antigens, more closely correlates human bronchial asthma and anaphylaxis, and I have no hesitancy in calling these reactions "experimental asthma."

Now, with reference to the question of antibodies. Dr. Alexander believes that there is growing evidence for regarding the anaphylactic antibody and the Prausnitz-Küstner antibody as one. It seems to me that it has been so conclusively demonstrated that doubt should no longer be entertained.

Dr. Alexander rightfully stated that one cannot do a test successfully on the guinea pig's skin. That is why we did not apply that particular test in our work. I will state, however, that positive transfers were obtained in human subjects with blood from animals in which we had induced experimental asthma, and concomitantly we produced passive anaphylaxis when this blood was transferred to other guinea pigs.

I do not know all of the comparative anatomy of the lower animal species, but I cannot understand how the guinea pig can have functioning mucous membranes if it has no bronchial mucous glands, as Dr. Alexander states. If a guinea pig has mucous membranes, I cannot conceive of its not having mucous glands.

DR. ALEXANDER.—If there are mucous glands and these are analogous to human glands, there should have been as much mucus in your pigs as in man with asthma.

DR. RATNER.—If an animal has mucous membranes he should have mucous glands. The question of the quantity of mucus present is merely a question of relativity.

Now, as to the pathology. If Dr. Alexander grants that there may be a spasm in the lung in human asthmatics, that is all I have contended. There is a bronchiolar spasm in a bronchial asthmatic reaction. Pathologic studies in cases of acute asthmatic deaths have shown that. That there may be mucous plugs and edema causing status asthmaticus or the death of the individual is merely a secondary factor, the accumulation of the secretion being due to the prolongation of the disturbed physiology resulting from the spasm. Why one cannot conceive of the existence of both mechanisms I do not know. I believe that the pathology of experimental asthma in the guinea pig and the pathology of asthma in the human being are the same. As in the guinea pig so in the hypersensitive human being, I believe the organ of predilection is the lung structure. We know that a canine type of anaphylactic death may occur in the human subject as well as the form found in the rabbit.

It seems to me that those who are opposed to this approach to advancing our knowledge of allergy should repeat my work on congenital sensitization and experimental asthma upon which I have been engaged for the past twenty years. Some have done it and borne out my findings. Perhaps actual experimentation would be more convincing than words.

Survey on the Incidence of Allergic Diseases in the General Population. W. C. SERVICE, M.D., Colorado Springs, Colo. (Abstract.)

A survey of a city of 35,000 population was made to determine the incidence of the more common allergic diseases in the general population. Sampling was based on an economic distribution. One thousand families were surveyed, comprising over 3,000 individuals. The present compiled data show that 44.9 per cent of the families surveyed have some form of allergic disease and 55.1 per cent are nonallergic; 19.68 per cent of individuals in the general population show some form of allergic disease and 80.32 per cent are nonallergic.

The distribution shows that 32.87 per cent of families have hay fever; 10.2 per cent of individuals show hay fever; 9.5 per cent of families have asthma; 3 per cent of individuals have asthma; 8.5 per cent of families have eczema; 2.65 per cent of individuals have eczema; 8.7 per cent of families have migraine; 2.7 per cent of individuals have migraine; 8.5 per cent of families have urticaria; 2.6 per cent of individuals have urticaria; 7.3 per cent of families have gastrointestinal allergy; 2.1 per cent of individuals have gastrointestinal allergy.

The cases are analyzed as to age, groups, and duration of the condition. From the standpoint of inheritance, 19 per cent showed maternal inheritance; 8 per cent paternal inheritance; 4.42 per cent inheritance from both paternal and maternal sides; 4.87 per cent gave unknown inheritance; and 64.6 per cent gave negative inheritance. The total inheritance factor was 31.42 per cent of the cases. The nonallergic families gave an inheritance factor of 6.5 per cent.

DISCUSSION

DR. ALBERT H. ROWE, Oakland.—This study by Dr. Service confirms previous reports and adds much additional information in regard to the frequency of allergy in the population at large. We must realize in such work that the conclusions are always open to possible error. Diagnosis of the allergic manifestations merely through conferences without the opportunity to confirm such opinions by results of treatment and prolonged observation is inevitably associated with some mistakes. Dr. Service has recognized this and has taken extra care in obtaining his information. The determination of gastrointestinal allergy and of allergic migraine is especially subject to error without every opportunity to study and treat the patient for an extended period.

My study of 400 students at the University of California about nine years ago initiated surveys of this type. Since then Vaughan, Jiménez, and others, have published more extensive studies. In analyzing such statistics it must be realized that the data can vary according to the location in which study is obtained.

Four years ago, I made another study of 2,000 students at the University of California during routine infirmary examinations. The data were obtained during one conference except in a few students with complicated histories. The statistics showed a family history of probable allergy in about 35 per cent. Checking with Dr. Service's results, this is probably lower than actually exists. All possible information in regard to the family history of allergy is difficult to elicit, especially in aunts, uncles, and grandparents. Thirty-three per cent showed a personal history of probable allergy; 3 per cent showed a history of possible past or present asthma which checks with Dr. Service's conclusions; 10 per cent have a history of hay fever which corresponds with his data. Probable eczema or allergic dermatitis occurred in 4.5 per cent of my subjects. Urticaria was reported by 13 per cent of my cases. This higher percentage may partly be accounted for by the large consumption of fruit in California. Of interest is the occurrence of poison oak in 40 per cent of my subjects.

Such statistics, as already stated, do not indicate the actual frequency of these allergic manifestations. The diagnosis too often is presumptive and it is usually made without skin reactions and without the results of therapy. However, the data are of great value, especially when the information is gathered with the care Dr. Service has used.

Is allergy increasing in the general population? Its apparent increase can be explained by the increased knowledge of allergy which is making physicians and the lay public more aware of the possible allergic manifestations.

Dr. George Piness, M.D., Los Angeles.—The survey presented is most interesting because Dr. Service approached it from a viewpoint different than any of the surveys heretofore made. He is deserving of much credit for the great effort and the large amount of work put into this study and the excellent results obtained by it. The sampling method of survey is a recognized and acceptable method, and we need have no hesitancy in accepting the results as authentic.

It was suggested by Dr. Nelson that we should try to get the PWA to make such a survey in every community. This is not a bad idea, as much valuable information could be obtained by it. The statistics reported by Dr. Service are quite in accord with the findings of most men who made surveys, with the exception of Balyeat, who reported such a large number of migraines as compared to those of others. When the reports of conservative workers, including the report of Dr. Service, are properly studied, one will know that the average of incidence is about the same for all communities regardless of size, location, or climate. He confirms the findings of the rest of us as to the age of onset, sex, etc.

Dr. Marion T. Davidson, Birmingham.—There have been surveys reported which were made in areas not so select as Colorado Springs, and some of the men who included the minor allergies have reported as high as 60 per cent of individuals having had some form of allergy.

About 50 per cent of my practice is composed of people sent to me for allergic study. It has been a long time since I made a complete allergic study on any one without finding some reactions. I always tell the patients that the mere fact that they give a positive reaction on the skin when a solution is injected into it, is in no way proof that that substance

is causing all the ills to which their flesh is heir. The clinical trial must be made or desensitizing treatment administered to prove any relationship between the positive skin test and the patient's complaints.

My experience here related causes me to believe that if tested to a sufficient number of potent solutions, every individual will give some allergic reactions. I also believe that every one is potentially allergic.

DR. FRENCH K. HANSEL, St. Louis.—In a survey of the type presented by Dr. Service, due consideration should be given to nasal allergy, as it is probably the most common manifestation. With the facilities he had, it was impossible for accurate diagnosis to be made in these cases. In otolaryngologic practice we have found that approximately 40 per cent of patients with nasal complaints have nasal allergy. Eighty to 90 per cent of the cases of chronic sinus disease are also of allergic origin. The inclusion of the nasal and sinus cases in statistical data would, therefore, result in a considerable increase in the percentage incidence.

DR. MERYL M. FENTON, Detroit.—I wish to say a few words about one of the references that Dr. Rowe mentioned regarding the work of Dr. Jiménez at the University of Michigan. I was associated with Dr. Jiménez for some time and understand the set-up of the University Health Service. He had the assistance of two laboratory technicians, several nurses, and a staff of about a half dozen students. The student enrollment at the University is about 13,000 each year, including the summer session.

The usual procedure consisted in having the freshman or matriculating student answer questions regarding family history of allergy, both major and minor. Cards were then sent out to selected cases inviting them to have the tests performed at a very minimal cost.

Dr. Jiménez has been carrying on this work for the past six or seven years, and during that time has published several interesting reports. Each student had a routine nasal smear, urinalysis, and blood count done at the time of the initial examination. It was found that approximately 30 to 35 per cent of the university students, which represents a cross section of the country, presented definite symptoms of allergy, with another 15 to 20 per cent representing potential allergy. The potential allergics had positive skin tests but no clinical history which indicated, according to our observations, a future clinical sensitivity. One of the freshman, who had come from Honolulu, was given an examination during his freshman year. At that time his nasal smear presented a marked eosinophilia and his skin test was markedly positive for ragweed. He had never been in contact with ragweed as far as could be determined. Within three years he developed a typical ragweed hay fever.

DR. BRET RATNER, New York.—The early work of Cooke and his coworkers indicated that the hereditary concept played a major role in allergy, and when I read Dr. Service's preliminary report, I had the feeling that he was going to disprove that concept.

There are many points that I should like to discuss, but one strikes me particularly. You say that about 30 per cent of the general population have allergy?

DR. SERVICE.—Twenty-two, major allergy.

DR. RATNER.—If this is so, how can there be such a small percentage of the families you studied which manifest allergy in the normal population?

DR. SERVICE.—Fifty per cent of families.

DR. RATNER.—I mean in the nonallergics. You said 9 per cent, I believe it was, of the families in nonallergic individuals who gave a history of allergy. Is that right?

DR. SERVICE.—Yes.

DR. RATNER.—If 30 per cent of the whole population have allergy, how can only 9 per cent of the families have allergy? Don't the 30 per cent allergic members belong to families? There are about 25 members in each family, consisting of three generations, and if 30 per cent of all the individuals have allergy—

DR. SERVICE.—Twenty per cent.

DR. RATNER.—How can there be only 9 per cent of the families that have allergy? There should be at least 20 per cent or more.

DR. SERVICE.—In surveying those individuals in the family, I did not include the family I was surveying. I took their past family history. If there was a child allergic and it had an allergic father, it was grouped as one family, and it was their past family heredity I was taking, grandfather and grandmother.

DR. RATNER.—Oh, you just took the grandparents. That is an important statistical error. Unless your data are comparable your conclusions cannot be valid. You should inquire into the same number of generations for each family; three generations is generally considered a fair sampling. If you should take a family history of three generations, including direct and collateral antecedents, you would find they average approximately 25 members today—you may get a positive family incidence, let us say, of 40 per cent. These same family histories will only give you a positive incidence of 22 per cent if you should include only direct antecedents. And if you inquire only into the history of parents, your figure will be closer to 9 per cent. I believe that your figure of 9 per cent positive family histories in the general population is incorrect, and it may be due to the manner in which your data were collected. I hope you will not consider me presumptuous if I suggest that you clear this point. Other investigators have committed this same error.

DR. MILTON B. COHEN, Cleveland.—I was much interested particularly in the graphs of the major incidence of the disease in the first decade, with the exception of one thing, migraine. That struck me as rather interesting because some of us find it rather difficult to classify many of the migraines definitely as allergic.

It would seem that here is further statistical information that even if migraine be allergic, there must be other factors influencing the signs in the records of Dr. Service, since we find that the incidence of all conditions we are quite definitely willing to admit to be allergic is in the one decade, and in migraine it comes very much later.

Investigations of heredity are very difficult. When you go out to obtain a family history, you have great difficulty in knowing what you are dealing with. I should like to cite for you an example of that that will illustrate it better than any statistical discussion.

Dr. Nelson and I were East a short time ago and we visited an allergist who was using the indirect method of testing. The passive transfer tests were being made on the mother's arm and we said, "We thought you always hired recipients, because you tell us that allergics do not give good passive transfer."

"Oh, but this is a nonallergic mother."

We looked at the mother and, according to what we think, her face had written on it that during her infancy she had had some disturbances which might have been allergic, so we said to the man, "You say this mother is nonallergic, and you are using her for your transfer, and drawing your conclusions. We think she is allergic."

"Well," he said, "question her."

I said, "Have you ever had asthma or hay fever?"

"No."

"What do your control tests show?"

The controls gave reactions to two pollens and to house dust.

You cannot go on the basis of subjective things. This question of heredity, in my opinion, will never be solved until we get some objective ways of determining from the examination of an individual whether he does not or does have some stigmas. If we could ever come to that point, and I believe we shall come to that point some day, then we will be able to go through a community and we will be able objectively as well as subjectively to determine the allergy and the antecedents. We can then find out whether Dr. Ratner is right, or the other people are right about this heredity.

Dr. Service.—In making these surveys, it is impossible to do all the work yourself. If you are going to survey a very large number of people, it is necessary to train someone. I selected two individuals who were themselves allergic and who were in the university and who I felt were capable, after a sufficient length of training, to carry on the survey as well as I could. I checked many of these cases personally.

Dr. Rowe, regarding the conferences, when it came to hay fever and asthma, I seldom saw those, but in the cases of migraine, eczemas, and urticarias, I saw at least half of the cases. If there was the slightest question, I interviewed them and tried by questioning to get an idea as to whether they belonged in the field of allergy.

The cases that we surveyed belong to what we consider to be entirely major allergies. None of the minor allergies were inquired into; that is, they were not summarized.

In the minor allergies the individual knows the cause of his symptoms, and, in the cases of urticaria we studied, we eliminated all those who knew the causes of their urticaria, and even the questionable ones, where they were almost certain but there was some slight question.

Dr. Cohen, the survey in the Springs was carried on largely during the months from last September until recently. Most of the summer visitors that we get there were not present at that time; as a matter

of fact, we eliminated from our survey the Broadmoor Hotel and the Cragmoor Sanatorium, and places where we might have conditions which might not be normal, and we tried to divide the city so as to take in only the resident population. Of course, I will admit, we have a good deal of hay fever in Colorado.

Dr. Hansel, as far as nasal allergy is concerned, I felt it would be absolutely impossible to go into that particular question. If I had had the possibility of studying by test methods these cases, we might have had a reason for going into nasal allergy, but on such subjective questioning, it is absolutely impossible to make an accurate analysis.

I appreciate Dr. Ratner's bringing up this question of heredity. I have probably erred there and will have to check the records and see what I can make of them.

Until we do have objective methods of studying problems of heredity, I do not feel that we can really gain much information on the subject.

Alcohol Susceptibility Test. JOHN M. NAGLE, Agnew, Calif. (Abstract.)

Individual differences in tolerance to ethyl alcohol have long been recognized. Experimental work in an attempt to establish a simple, yet accurate, test to demonstrate the degree of tolerance is herein described.

Method and Results.—Hundreds of persons, alcoholics and nonalcoholics, have been subjected to the following simple intradermal skin test:

Three-tenths cubic centimeter of a solution, containing ethyl alcohol, 95 per cent U.S.P., and distilled water 6:4 (approximately 60 per cent) is injected into the skin of the lateral aspect of the deltoid region. An equal amount of physiologic saline is used as control. No skin antiseptic is used.

A wheal, about 9 mm. in diameter, is common to all. The significance of the test is the degree of surrounding erythema. Unlike the wheal, this manifestation is not common to all. Readings are made in twenty to thirty minutes. They are constant on successive days.

The observation falls under one of six headings: No redness (zero reaction); very slight (±); slight (+); mild (++); moderate (+++); and marked (++++).

The phenomenon begins to disappear in about sixty minutes.

Interpretation.—This test is associated with individual tolerance in varying degrees as follows: 0 = maximum; ± = very good; 1+ = good; 2+ = fair; 3+ = poor; 4+ = least.

The above relationships were determined following the ingestion of alcoholic beverages by males and females coming within the various groupings.

The amount of beverage ingested ranged from an alcoholic equivalent of 2.5 ounces in the 0 group gradually downward to 0.25 ounce in the 4+ group. The pharmacologic response was the same in all groups. Therefore, it can be plainly understood how one possessing the least tolerance, or 4+ reaction, is beyond his or her tolerance (psychologic—

not physical impairment) after the ingestion of 1 ounce of stronger spirits. However, if that same person remains within his tolerance, he can still partake without undue effect.

Application.—Immediate: The alcohol susceptibility test is a diagnostic and therapeutic aid, and can serve as a valuable adjunct in the treatment and regulation of alcoholic beverages in individuals who want aid, and who are capable of utilizing it.

Future: Through educational means, the test may be described before groups of college students, etc., so that one's tolerance may be more accurately estimated.

Medicolegal: Professor Sachsenberg* of Germany recently demonstrated that any law attempting to establish psychologic impairment by means of body fluid analysis following ingestion of alcoholic beverages is inadequate. Individual difference of tolerance of ethyl alcohol must also be recognized. The test described above would be a simple means of supplying this factor.

DISCUSSION

Dr. W. H. Manwaring, Stanford University.—As I understand Dr. Nagle's paper, he thinks he has established three facts: First, that there are quantitative differences in the local reactions of different individuals to endermically injected ethyl alcohol. At one end of his scale there are some individuals in whom intense inflammatory reactions take place 2½ to 3 inches in diameter surrounding the central wheal. Individuals reacting with this size and intensity to his routine test dose are designated by him as ++++ allergic to ethyl alcohol. About 20 per cent of his control population belong to this group. At the other end of his scale, about 10 per cent of his selected population gave no peripheral inflammatory reaction whatsoever to his arbitrary test dose. These 10 per cent belong to his alcohol tolerant or relatively immune group.

Dr. Nagle's second point is his assumption that there are wide variations in individual susceptibility to ingested alcohol. This is in accord with popular belief, but is not generally endorsed by pharmacologists, who have been unable to demonstrate such individual differences in laboratory animals. They, therefore, would explain apparent differences in individual susceptibility as presumably due to different rates of absorption from the gastrointestinal tract.

That Dr. Nagle is correct in his assumption, however, has been shown conclusively by recent German investigators. The Dresden Alcoholic Commission,† for example, made very careful quantitative determinations of blood alcohol in many hundred individuals, with a parallel determination of psychologic disturbances. They found that 20 per cent of the selected individuals were incapacitated for safe automobile driving as soon as the alcohol content of the blood stream had reached 0.02 per cent (0.2 c.c. ethyl alcohol per liter). This is equivalent to the alcohol content of one small bottle of beer, assuming that the ingested alcohol is completely absorbed into the blood stream. These individuals evidently have nervous tissues markedly hypersensitive to ethyl alcohol.

*J. A. M. A. **110**: 1617, 1938.

†Foreign Letters (Berlin): J. A. M. A. **110**: 1617, 1938.

At the other end of the Dresden scale, 10 per cent of their selected individuals remained perfectly sober even after the alcohol content of the blood stream had been increased to six times this amount, i.e., to 1.2 c.c. per liter. The nervous tissues of these individuals are evidently relatively tolerant or immune to ethyl alcohol.

Dr. Nagle's third point is his belief that his skin test is a direct measure of the alcohol susceptibility of the nervous system, an individual with a highly sensitive skin having the same degree of psychologic allergy to ingested alcohol. Ten years ago most clinical allergists would have accepted this as axiomatic. At that time it was generally believed that the skin test is both a qualitative and quantitative measure of the sensitivity of all other organs and tissues of the body. During the last decade, however, it has been shown that skin sensitivity may exist in individuals with apparently normal bronchial musculature, or that the opposite may be true.

Remembering our own earlier mistake, I believe most allergists today will be inclined to be skeptical of Dr. Nagle's hypothesis until the hypothesis is confirmed by other investigators and supported by more nearly adequate laboratory and clinical evidence. If confirmed, however, Dr. Nagle's communication may mark a new era, both in the social control of alcoholism and in the fields of theoretical and clinical allergy.

Dr. Frank Perlman, Portland, Ore.—I had an occasion recently to test, by the scratch method, first, a patient who was suffering from bronchial asthma, and, surprisingly enough, on almost all of the tests she showed a very large wheal that showed many pseudopods. I thought she was a patient who was highly allergic. Yet, on intradermal testing with Coca's solution as a solvent, she showed almost no reactions, and the result proved that the alcohol used produced the reactions entirely. That was brought out by the fact that we found when no antiseptic was used, or when some other antiseptic was used, such as hexylresorcinol, no reaction occurred in the presence of the allergens.

THE JEWISH HOSPITAL OF BROOKLYN

ALLERGY DIVISION, BROOKLYN, N. Y., NOVEMBER 21, 1938

Studies in Silk Hypersensitiveness. MURRAY ALBERT, M.D., and MATTHEW WALZER, M.D. (Abstract.)

The materials employed in this study were made from silkworms taken from dried cocoons. The worms were ground into a fine powder and were rendered fat-free by repeated extraction with ether. The residue was powdered and mixed with petrolatum to form a 25 per cent ointment. A bit of this was applied to the skin of the upper arm and covered with a square of adhesive plaster, the center of which was lined with wax paper. After forty-eight hours, the excitant was removed from the skin. The site of contact was inspected at forty-eight hours, seventy-two hours, and at various intervals thereafter.

A large series of tests was performed with this material on atopic and nonatopic children and adults. At the sites of application, reactions occurred which differed in appearance from the usual type of contact reactions obtained with oils, dyes, etc. The lesions were very superficial and, as a rule, sharply circumscribed. They consisted of closely aggregated, shiny, discrete vesicles, which were pin point in size. Erythema was not a constant factor in these reactions, but when present, was pinkish and localized to the vesicular area. A slight degree of induration was occasionally present. Neither pigmentation nor necrosis occurred in these reactions. In a group of 61 atopic children, 62.3 per cent showed the above type of reaction at the site of a forty-eight-hour contact with a 25 per cent silk ointment. Using an undiluted saline extract of silkworm containing 2.4 mg. nitrogen per c.c. as the contactant, 58 per cent of positive reactions were obtained in the same group of patients. In a series of 46 nonatopic children tested with the 25 per cent silk ointment, only 6.5 per cent showed positive reactions. Among 52 atopic and nonatopic adults only one positive reaction was found.

In many instances positive reactions did not appear after the first application, but did appear after two or more applications, applied at intervals, to different sites. In these instances hypersensitiveness was undoubtedly induced by the applications.

There was no constant relationship between the contact type of reaction and the reaction obtained by an intracutaneous test with a saline silk extract. The contact reaction often occurred in the absence of the atopic reagin antibody and vice versa. With one exception, all

of the patients showing a positive reaction to the silk ointment gave negative reactions to patch tests with silkworm oil. Reactions were also obtained in atopic children with 25 per cent ointments of cottonseed, goat, wool, and ragweed, prepared in a manner similar to that employed for the silkworm. The incidence of these reactions was much lower than that found with the use of the silk preparation. Nonatopic children and adults rarely reacted to contact with these substances.

Individuals showing positive reactions to the above ointments almost invariably failed to give positive patch tests to the oils obtained from the same sources. The active excitant in this form of hypersensitiveness, therefore, appeared to be in the protein fraction.

Active Sensitization in Humans With Trichina Antigen. BESSIE BARON, B.A., and MATTHEW BRUNNER, M.D. (Abstract.)

The purpose of this study was to determine whether diagnostic skin-test doses of trichina antigen could sensitize patients to this antigen.

Saline trichina extracts were prepared from rabbits infested with *Trichinella spiralis* larvae. The subjects studied were 18 atopic patients, varying from 4 to 44 years of age, who gave negative reactions to an intracutaneous test with 0.01 c.c. of trichina extract containing 0.01 mg. nitrogen per c.c. They were then repeatedly treated with 0.1 c.c. intracutaneously of a solution containing 0.1 mg. nitrogen per c.c. These injections were given at intervals of from one to two weeks over a period varying from four to twenty weeks. Skin reactions were read within fifteen minutes after testing.

The onset of sensitization was marked by a slight reaction consisting of an increase in the size of the wheal or erythema. It was noted after the first, second, third, or fourth skin-test doses in 15 out of 18 cases (83 per cent). Definite marked reactions occurred after the third, fourth, or fifth skin-test doses in 6 out of 18 cases (33 per cent). Ten (56 per cent) of 18 cases showed marked reactions by the ninth dose.

The sensitivity to trichina extract was found to be mediated by the atopic reagin antibody. On cutaneous sites prepared with sera obtained from subjects sensitized to trichina, slightly stronger reactions were obtained with ascaris than with trichina antigen. The same was true on sites sensitized with human ascaris serum.

The latter finding indicated that there is a common antigen in ascaris and trichina which is much stronger in the former than in the latter. From a practical point of view, it is important to remember that the diagnostic value of intracutaneous trichina tests diminishes with their repetition in any single patient.

The Spontaneous Activation of Negative Test Sites in Experimental Contact Dermatitis. MAX GROLNICK, M.D. (Abstract.)

This report deals with the phenomenon of spontaneous "flare-up" or activation of previously negative sites of application of an excitant in actively induced contact dermatitis in man. In 18 subjects in whom sensitivity had been induced by the application of a single patch test of *Krameria* left in contact with the skin for a period of from one to seven days, reactions occurred on the eighth to the twenty-first day. In 4 subjects sensitized by a one-day application of poison ivy extract, reactions occurred on the seventh to the twenty-first day. This interval between the first skin contact with the excitant and the "flare-up" of the site is the incubation period for sensitization. In 19 subjects in whom from two to five applications of *Krameria* at intervals of one or more weeks were needed to sensitize, there occurred a spontaneous activation or "flare-up" of the preceding site of application in from one to eleven days following the appearance of a reaction at the final site of application. These sites reacted after having been negative for a period of from ten to thirty-four days. In 4 of the 19 subjects there were "flare-up" reactions on two of the preceding sites of application. These sites had been negative for from twenty to forty-three days.

These experiments demonstrate that the *Krameria* excitant can be fixed locally for as long as forty-three days before the sensitizing process is sufficiently active to cause a reaction at the respective sites. It was also noted that the "flare-up" of negative test sites always occurred in the reverse chronologic order of their application to these areas.

The "flare-up" phenomenon may be regarded as an indication of active sensitization of the individual to the excitant.

The Coincidence of Positive Cutaneous Reactions to Various Pollens in 500 Cases of Hay Fever and Its Significance. MAX HARTEN, M.D., and KATHERINE L. BOWMAN, A.B. (Abstract.)

Five hundred hay fever cases were tested intracutaneously with the pollens of timothy, plantain, ragweed, and with a tree mixture (equal parts of ash, birch, beech, oak, poplar, and hickory). Testing was performed on the outer aspect of the upper arm with dilutions of the various pollens beginning with 0.0001 mg. nitrogen per c.c. and not exceeding 0.1 mg. nitrogen per c.c.

A remarkably high coincidence of positive reactions to timothy, ragweed, plantain, and trees was found. Only 11 totally negative reactions were obtained in 6 cases among the 2,000 tests performed on the 500 patients. These included 2 negative reactions to timothy, 3

to ragweed, 2 to plantain, and 4 to trees. In the 4 instances where these negative cutaneous reactions were checked by passive transfer no reagins were found. The 1989 (99.4 per cent) positive reactions included 191 (9 per cent) which were less than slight or slight in degree, and 1,798 (90 per cent) which were greater than slight. The slight and less than slight reactions were confirmed by passive transfer in all of the 36 instances in which it was attempted. Of 56 greater than slight reactions checked by passive transfer, 54 were corroborated.

One hundred atopic patients not clinically sensitive to pollens were also tested with the 4 pollen extracts. Thirty-seven showed *uniformly negative* reactions to timothy, ragweed, plantain, and trees. Fifty-five showed *uniformly positive* reactions to these pollens. In 8 cases there was a lack of uniformity in the pollen reactions. In this series of 100 cases, passive transfer tests corroborated the results of the direct tests in 71 of the 72 instances in which transfer was attempted.

Two sera obtained from hay fever patients in Hawaii showed no uniformity of positive passive transfer reactions to the 4 pollen extracts.

From the above evidence it seems unlikely that the high coincidence of positive cutaneous reactions to pollens observed in hay fever cases can be explained by assuming that there is a common antigen in all pollens. It seems more reasonable to assume that active sensitization to pollens occurs to a variable degree following contact, in all atopic individuals in whom there is an hereditary predisposition to sensitization with pollens.

SOCIETY FOR THE STUDY OF ASTHMA AND ALLIED CONDITIONS

Resolutions

WHEREAS, the Society for the Study of Asthma and Allied Conditions has learned of the tragic death of Dr. Salvatore Parlato, and

WHEREAS, the Society has suffered the loss of one of its most beloved and most honored members, and

WHEREAS, his amiability, his industry, and his character were an inspiration to all who knew him, and

WHEREAS, his contributions to the field of Allergy and Immunology will remain outstanding, long into the future, be it

Resolved, That we, the Society for the Study of Asthma and Allied Conditions, formally and sincerely record the realization of our misfortune in his untimely passing, and be it further

Resolved, That a copy of these resolutions be spread upon the minutes of the Society, that a copy be forwarded to his wife and his family, and that a notice be printed in the JOURNAL OF ALLERGY.

WARREN T. VAUGHAN, President
HOWARD J. OSGOOD
W. C. SPAIN

Annual Review

ALLERGY AS RELATED TO OTOLARYNGOLOGY AND OPHTHALMOLOGY

Literature for 1938

French K. Hansel, M.D.
St. Louis, Mo.

A REVIEW of the literature on the subject of allergy from the standpoint of ophthalmology and otolaryngology for the year of 1938 shows a comparatively small number of presentations devoted to this subject. In general, there appears to be an increasing interest in the part played by allergy in paranasal sinus disease. There are, however, far too many articles on the subject in which allergy is given no consideration whatsoever. On the other hand, in those instances in which allergy is considered, there are definite indications that often allergic management has not been adequate. There is great need for better cooperation between the allergist and the otolaryngologist. Only by this cooperation can certain important factors be determined. For example, further statistical studies should be made on the incidence of allergy among nasal and sinus cases in general and on the incidence of polypoid or hyperplastic changes in nasal allergy, hay fever, and asthma. The frequency of reversible as compared with irreversible changes in these cases should also be determined. The comparative incidence of acute and especially chronic infections and more definite indications for radical surgery remain yet to be estimated.

The recent report of Watson and Kibler on the subject of allergy as related to bronchiectasis should stimulate widespread interests among allergists, rhinologists, and internists.

Comparatively few papers have appeared on the relation of allergy to ophthalmology. Jones[1] reports a case of Dermatitis venenata in the use of physostigmine salicylate in the eye. It caused burning, itching, and edema of the upper and lower lids. A positive test to physostigmine salicylate was obtained within forty-eight hours after application to the skin.

In the study of a case of conjunctivitis reported by Simon,[2] the following evidence indicated that the chief etiologic factor was an allergic reaction to the spores of air-borne fungi. Seasonal variations in the patient's symptoms coincided with seasonal variations in the atmospheric concentration of fungus spores. Changes in the patient's geographical location were accompanied by changes in his symptoms. Skin

tests with fungus extracts were definitely positive. The clinical symptoms of conjunctivitis were reproduced by the application of fungus extract to the conjunctiva. The control test in a non-sensitive subject was negative. The patient was exposed to fungus spores in that these were cultured in abundance in his home. Hyposensitization with fungus extracts was followed by the relief of symptoms.

Prewitt[3] reports a case of retinal detachment probably of allergic origin. The patient, a man aged 62 years, gave a past history of urticaria and angioneurotic edema. Previous to complete retinal detachment, several attacks of transient blindness occurred which were usually associated with generalized angioneurotic edema and urticaria. On one occasion following the ingestion of turkey liver, he developed a marked edema of the jaws and cheeks, accompanied by large blebs on the cornea of the left eye.

It is interesting that passive transfer of hypersensitiveness can be demonstrated to mucous membranes as well as to skin. Gray and Walzer[4] have shown in previous studies that the mucous membranes of the eyes and nose of normal individuals can be passively and locally sensitized by injections of human reagin-bearing serum. In the present study they demonstrated that the rectal mucous membranes can also be passively and locally sensitized in the same manner. The allergic reactions were manifested by edema, hyperemia, and increased mucous secretion in the sensitized area following the oral and rectal administration of the specific antigens.

Extensive investigation on the biochemical changes in the blood in allergy have shown no significant alterations. On the other hand, studies of nasal and bronchial secretions have shown definite variations in the pH and percentages of electrolytes under various conditions of allergy and infection. It is significant that considerable amounts of calcium are lost in allergic secretions. Much also remains to be known about lysozyme and other enzymes, antibodies, and possibly hormones, in nasal and bronchial secretions.

Daly[5] has shown that lysozyme is present in normal nasal mucus and has described a method of obtaining sterile preparations from it. His experiments showed that nasal lysozyme in sufficient concentrations caused *Staphylococcus aureus, Streptococcus hemolyticus,* and pneumococcus III to grow in a granular manner. In one experiment pneumococcus III suffered some loss of virulence as a result of contact with nasal lysozyme. Although the results of these experiments on pneumococcus III were considered inconclusive, they seem worthy of note, since they are in agreement with the findings of others.

Buhrmester's[6] report represents further studies on the hydrogen-ion concentration of nasal secretions in various diseases of the respiratory tract. In all, 350 determinations were made on 125 patients. The

conditions presented were as follows: 6 had atrophic rhinitis; 11 had bronchoscopic treatment; 25 had colds; and 83 had nasal allergy, complicated or uncomplicated by infection. It was noted that loss of weight is reflected in the nasal secretion by an increase in the hydrogen-ion concentration. The secretion during colds is alkaline in the initial stage, and the pH decreases to normal as clinical improvement takes place. She finds that the initial physiologic response of the nasal mucosa to stimulation is similar, regardless of the inciting agent.

The general enthusiasm regarding the use of ionization in nasal allergy has almost completely disappeared, indicating that this method of treatment is no longer being employed on a large scale. But with the introduction of ionization as a treatment for nasal allergy, interest was stimulated in the use of escharotics, astringents, and other agents.

Abramson[7] reports his experiences with the use of tannic acid therapy in allergy of the nasal mucosa. He uses a solution of 0.5 per cent tannic acid which the patient sprays into the nose with a glass nebulizer two or three times a day, depending upon the reaction. In some instances the tannic acid solution causes too much irritation and, therefore, must be used only in selected cases.

For those cases of nasal allergy refractory to other methods of treatment, Fishof[8] recommends the use of injections of sodium morrhuate into the inferior turbinates. After cocainization of the mucosa, 0.25 to 0.5 c.c. of 5 per cent solution of sodium morrhuate is injected between the periosteum of the turbinate and the overlying mucosa. Injections may be given at several points in the turbinates at the same time. Small amounts of fluid are injected at each point. The technique and results obtained were illustrated in seven case reports. On the whole, the results obtained were considered most satisfactory.

Hollender and Fabricant[9] present a very comprehensive histologic study on the nasal mucosa following nasal ionization. No histologic evidence has been produced to prove that nasal ionization is a harmful therapeutic procedure. They conclude that the evaluation of this procedure should be based solely on clinical observation until more definite histologic evidence of the effects of nasal ionization is available.

From a review of the current literature, Hansel[10] summarized the status of ionization in nasal allergy. On the basis of this review, the following conclusions were drawn: According to the observations of many leading rhinologists, ionization of the nasal mucosa is considered a safe and satisfactory measure in the treatment of hay fever and perennial nasal allergy. On the other hand, the observations of several leading allergists indicate that ionization does not give results comparable to those obtained by allergic methods of treatment. Several observers have shown that the use of escharotics in nasal allergy will produce results equally as satisfactory as those obtained by ioni-

zation. So far, no permanent destructive changes have been noted as a result of ionization. Complications, such as anosmia, neuralgia, and sinusitis, however, have been reported in a few cases. Satisfactory relief following ionization is apparently the result of a general desensitizing effect as well as a shrinkage of the nasal tissues and the diminution of hypersecretion. It was emphasized that accuracy in diagnosis in all patients subjected to the various types of treatment discussed is essential in order to eliminate errors in the compilation of results on a statistical basis. It is generally concluded that ionization in nasal allergy should be confined to cases in which allergic methods of treatment have failed to give satisfactory relief of symptoms. The selection of cases for this type of treatment, therefore, should be made by the close cooperation of the allergist and the rhinologist.

The high incidence of allergy among nasal and sinus cases in general is being more commonly recognized by rhinologists. According to the observations of Swann,[11] from 20 to 30 per cent of sinus disease is of allergic origin, and in cases of chronic disease the incidence of allergy is much greater. Any patient with a history of frequent colds, sneezing, itching of the nasal mucous membrane, nasal discharge and nasal obstruction, edema, and pallor of the mucous membranes should receive a thorough study to determine the possibility of the presence of nasal allergy.

Although inhalants play an important part in the etiology of nasal allergy, foods may also act as excitants. Eyermann[12] reports his observations on a group of 181 patients in whom the deliberate ingestion of food induced nasal obstruction, coryza, and sneezing. From his observations he concludes that multiple skin test and clinical sensitivity are the rule rather than the exception and that skin sensitivity is not an unerring guide to clinical sensitivity. He found that the foods most frequently eaten are the ones most likely to induce attacks of nasal allergy. Frequently, food and inhalant avoidance is sufficient to bring about a satisfactory therapeutic result. He emphasizes that in patients with perennial nasal allergy and hay fever, avoidance of food and inhalants other than pollen usually brings about a satisfactory therapeutic result. He found that when bronchospasm complicates the allergic reaction in the nose, inhalants are more likely to be the dominant causative agents. Before determining that pollen injections are imperative, one should consider the clinical influence of foods and inhalants other than pollen. In many of these cases he feels that the persistence and duration and possibly the initiation and intensity of symptoms depend upon the total allergic dose.

In the management of nasal allergy it is difficult to explain the discrepancy in various reports of the evaluation of the causative factors

in these cases. For example, in the following presentation, food was not found to be the sole factor in a single case.

Winkenwerder and Gay[13] report an analysis of 198 cases of perennial allergic rhinitis encountered in private practice. They found that nasal allergy occurs in all age groups, being most common in young individuals, especially before the age of 10 years. During the first decade males predominated but after this period the disease was more frequently encountered in females. It seems rather unusual that only 12 out of 100 patients showed a blood eosinophilia. Approximately 25 per cent of the cases were associated with bronchial asthma, 20 per cent with hay fever, 5 per cent with eczema, and 3 per cent with urticaria. In less than 2 per cent food sensitivity was demonstrated. About 50 per cent of the associated allergic disorders appeared during the first decade. It was stated that dust, feathers, and orris root, singly or in combination, accounted for 95 per cent of the etiologic factors in the cases in this series. Animal danders, kapok, and cottonseed accounted for the remaining 5 per cent. It is noteworthy that the observers failed to find a single case in which food was the only causative factor. One hundred and thirty-seven patients were treated by avoidance of the offending factors and by desensitization with specific extracts. In 82 per cent the patients were completely cured or markedly improved; in 18 per cent they remained unimproved. Of 22 cases in this series that showed coexisting infections of the sinuses or tonsils, 11 cleared up following allergic management while 9 required surgical treatment.

In the diagnosis of nasal allergy from the standpoint of otolaryngology, a great deal of emphasis should be placed upon a complete investigation of the local condition. In treatment the recognition and attention to other associated manifestations of allergy should not be overlooked.

In discussing the diagnosis of nasal allergy, Hansel[14] emphasizes a careful analysis of the nasal symptoms and repeated cytologic examinations of the nasal secretions for eosinophiles. Further emphasis is placed upon the correlation of the cytologic picture with the x-ray and bacteriologic findings. Attention is also called to the importance of recognizing acute and chronic infections as complications of allergy in the nose and paranasal sinuses. In the complete analysis of patients with nasal allergy, attention should also be directed to the association of other manifestations of allergy, such as gastrointestinal allergy, allergic headache, and the many types of skin allergy. The various types of allergy of the nose and paranasal sinuses, with their pathologic changes and their association with other manifestations of allergy, are illustrated in 10 case reports.

The pathologic changes in the nose and paranasal sinuses in allergy may be of the reversible or irreversible type. Reversible changes are

those which disappear with the control of allergic symptoms. Acute or subacute edema in the form of polyposis, which may occur in the nose and sinuses in hay fever, almost invariably disappears at the termination of the hay fever season in purely seasonal cases, provided that complicating infection has not developed. In hay fever patients with perennial symptoms, these changes may persist, depending somewhat upon the degree of allergic reactivity.

In the usual perennial cases reversible or temporary edema may coexist with irreversible or permanent edema. Until allergic management has been effective in controlling the symptoms, it is, therefore, impossible to evaluate the relative degree of these two types of pathologic change. Finally, cases with permanent changes or fixed edema, with cystic degeneration and superimposed infection which undergo little change under allergic management, represent the types that should be subjected to radical surgical procedures.

It has been estimated that the average incidence of polyposis among all types of nasal allergy is about 25 per cent. The approximate percentage of the reversible and irreversible types has not as yet been determined. This can be accomplished only by close cooperation of otolaryngologist and allergist. In all patients subjected to surgical interference, histopathologic findings should be correlated with all other data.

In a very comprehensive presentation, Semenov[15] discusses the surgical pathology of nasal sinusitis based on a group of 500 surgical cases. Microscopic examination of the mucosa showed that when thickening in excess of 2 mm. is present, it is associated with deep seated degenerative changes in 50 per cent of the cases. Of the 500 cases, Semenov classified 72 per cent as purulent sinusitis and 28 per cent as nonpurulent hyperplastic polypoid and cystic degenerative. Manifest allergic sinusitis occurred in 17 per cent; 35.4 per cent were classified as equivocal allergic cases. These latter were considered as latent allergic conditions in which the history was uncertain, vague, or incomplete, but in which microscopic examination showed tissue eosinophilia associated with other histologic findings sufficient to warrant a presumptive diagnosis of latent allergy. Nonallergic inflammation, as determined by careful history and examination and histologic preparations, was present in 47.6 per cent of the cases. Degenerative changes were more pronounced in allergic sinusitis. He states that hyperplastic sinusitis, especially the bilateral type, is allergic in 70 per cent of the nonpurulent cases.

Tissue cultures revealed a preponderance of streptococci and staphylococci in chronic sinusitis, mixed infection being present in 80 per cent. It was further found that exudative sinusitis usually responded to conservative treatment. Degenerative changes which are irrever-

sible in character required radical treatment. A study of postoperative healing in the paranasal cavities showed that it is accomplished by the formation of a dense layer of white fibrous connective tissue which epithelizes by an ingrowth of nasal mucosa.

In a discussion of bronchial asthma and nasal allergy, Ramirez[16] considers the relationship of the pathologic changes in the nose and paranasal sinuses to asthma. He states that the exact relationship between nasal and sinus findings in asthma are often difficult to determine. Although they may bear no relationship to each other, he believes that both may be of allergic origin and caused by the same allergen as in pollen asthma associated with hay fever. Furthermore, they may be due to entirely unrelated substances. In the diagnosis of allergy, Ramirez emphasizes the necessity of a complete and carefully taken history, thorough physical examination, complete laboratory and roentgen analysis, as well as tests for sensitization. As for treatment he places importance upon allergic management and then to possible surgical interference in the nose and paranasal sinuses when the pathologic conditions appear to be definitely related to the asthma.

The relationship of pathologic changes in the nose and paranasal sinuses to bronchial asthma has been a much discussed subject. Some observers feel that the lesions in both shock organs represent one and the same coexisting process and that the nasal and sinus changes do not play an important part as the actual cause of asthma. A few statistical studies of this relationship, particularly from the standpoint of surgical operations on the sinuses, have tended to substantiate the former viewpoint.

Weille[17] presents his observations on the condition of the nose and throat in 500 cases of asthma. Almost half of the patients were between the ages of 30 and 50. Sinusitis was present in 362 cases. Among 290 patients who had no drainage of the sinuses, bronchoscopy, removal of polyps or of teeth, tonsillectomy, or other operation, 142 had slight or severe sinusitis, 15 had pansinusitis, 18 had infected, 20 severely infected, tonsils, and 25 had abscessed teeth that were untreated. About two-thirds were improved or cured. The rest remained the same or became worse.

Bronchoscopic examination in doubtful cases of asthma is frequently of indispensable value in diagnosis, especially in instances in which the typical eosinophilia of the bronchial secretions and other symptoms and signs are lacking. Pollak, Cohen, and Gnassi[18] present a very comprehensive review of the literature on inflammatory bronchial tumors. The increasing recognition of these lesions is a result of the greater use of the bronchoscope and the increasing knowledge of the mechanical and biologic sequelae of these lesions. Since dyspnea is often an outstanding symptom in such cases, they must not be erroneously diagnosed as bronchial asthma.

Bronchiectasis is not an infrequent complication of bronchial asthma. On the other hand, chronic bronchitis and bronchiectasis may occur in the absence of definite asthma. Polypoid changes in the nose and paranasal sinuses similar to those noted in cases of allergy commonly coexist in patients with bronchiectasis without asthma. Few observers have paid any particular attention to the incidence of allergy in these instances. The changes in the nose and sinuses and the bronchi have been treated on an infectious basis. Patients with pathologic changes in the sinuses have been subjected to surgical procedures because of the possible etiologic relationship of the two conditions. Now the question arises as to the possible part played by allergy in bronchiectasis with or without coexisting sinus changes.

Fifty consecutive cases of asthma of a duration varying from three to ten years were studied by Viswanathan[19] with the idea of determining the incidence of bronchiectasis. Roentgenograms were taken on all patients with the use of iodized oil. Fourteen showed definite evidence of bronchiectasis, 6 showed saccular dilatation, 5 cylindric dilatation, and 3 early bronchiectasis, with tortuosity of bronchioles and slight cylindric dilatation. Ten of the 14 patients presented clinical evidence of chronic bronchitis with asthma, but the history was suggestive of the primary condition being asthma.

The incidence of sinusitis in 217 patients with bronchiectasis, exclusive of congenital bronchiectasis or with bronchiectasis due to a foreign body, was investigated by Walsh and Meyer.[20] Among the 217 patients, 145, or 66.8 per cent, showed associated sinusitis. Various symptoms and illnesses, such as influenza and pneumonia, preceded the apparent onset of the bronchiectasis. The process involved both lungs in 109 cases, the bases alone being involved in 99 of these. The 36 remaining cases had unilateral involvement. There was no predominance of disease of the right lung over that of the left. Forty-two patients showed only mild bronchiectasis; in 81 the disease was moderately advanced, and in 22 the condition was far advanced. The extent of sinus involvement was variable, and there was no relation between the degree of sinusitis and the degree of bronchiectasis. Chronic pansinusitis or gross bilateral infection of the antra were noted in 78 cases. Most of the 72 patients who presented no evidence of sinusitis attributed the onset of bronchiectasis to definite disease or symptoms. In 29 cases the cause was unknown. Nineteen dated their illness from pneumonia and 7 had had influenza. Only 14 per cent failed to give a history of disease of the respiratory tract at some time in the past. Both lungs were involved in 39 instances of bronchiectasis without sinusitis. In 34 unilateral cases without sinusitis, the right lung was involved nineteen times and the left lung fifteen times. In 23 cases the degree of bronchiectasis was mild; it was moderately advanced in 45, and far advanced in 14.

The part played by sinusitis in 75 cases of bronchiectasis was investigated by Goodale.[21] On the basis of x-ray evidence, 46 patients had chronic sinus infection and 29 had negative sinuses. Among the 29 negative cases, 18 gave a history of clinical evidence of sinusitis, either a recurrent acute sinusitis or a mild chronic sinusitis. In 11 cases, or 14.5 per cent, sinusitis did not appear to play a part in the onset or subsequent course of the bronchiectasis. In the majority of the patients the bronchiectasis followed infections of the upper part of the respiratory tract. Pneumonia alone accounted for 25 cases. Goodale found that the prevalence of sinus infection paralleled the extent of the bronchiectasis. The sinuses were infected in 40.7 per cent of those in whom only one lobe was involved and in 73 per cent of those with more than one lobe involved. It was further stated that once the patient has acquired a chronic sinusitis, the chances of further damage to the lungs is increased because of the susceptibility to repeated infections of the respiratory tract.

The above-mentioned reports are representative of many observations made during the past several years on the subject of sinusitis and bronchiectasis. The study of the cytology of the secretions for eosinophiles has not been utilized as a diagnostic procedure in these cases nor have they been investigated from the allergic standpoint. There is much need, therefore, for further studies on the possible incidence of allergy in bronchiectasis. The recent report by Watson and Kibler emphasizes this important relationship.

Watson and Kibler[22] noted that bronchiectasis is seldom found without at least some evidence of sinusitis. They also observed that many cases of bronchiectasis had some manifestations of allergy, such as hay fever, asthma, urticaria, eczema, or rhinitis. Upon studying the cytology of the nasal secretions, they were impressed with the frequency of the high percentage of eosinophiles. A similar study of the sputum likewise showed an abundance of eosinophiles in a large percentage of the cases of bronchiectasis. On this basis they began the investigation and treatment of these patients from the allergic standpoint and were able to obtain most satisfactory results. Thus, a new conception of the etiology of bronchiectasis which makes its prevention and recovery possible has been presented. They found that bronchiectasis may frequently be successfully combated in its earlier stages if considered a sequela of allergic bronchitis. In view of the fact that many patients with chronic sinus involvement and bronchiectasis seek the warm dry climate of Arizona for relief, Watson and Kibler have had an unusual opportunity to observe many cases of this type.

They have noted that patients with bronchiectasis frequently have hay fever, eczema, moderate but definite asthma at times, or other manifestations of clinical allergy. Among all patients with bronchiectasis it was observed that in general there was an abnormally

high percentage of eosinophiles in the bronchial secretions, that is, 10 per cent or more. In fully 90 per cent of the cases, a definite diagnosis of allergy could be made on the evidence found.

Watson and Kibler[23] divide all bronchiectasis into these classes: (1) Congenital bronchiectasis; (2) mechanical bronchiectasis, as accompanying tuberculosis, thoracoplasty, fibrous pleuritis, pulmonary fibrosis, etc.; and (3) allergic bronchiectasis.

In studying bronchial disturbances by x-rays with iodized oil, cytologic examination of sputum and nasal secretion, and cutaneous testing, four types of cases were encountered, as follows: (1) Cases diagnosed as bronchiectasis, with chronic cough, purulent sputum, basal lung râles with no x-ray evidence of bronchial dilatation as shown with iodized oil, but only basal allergic bronchitis. Symptoms in these cases often existed for ten years or more. (2) Cases similar to the first type in which slight bronchiectasis exists, as evidenced by lack of tapering of the descending small bronchioles. (3) Cases with moderate bronchiectasis. (4) Cases with far-advanced bronchiectasis, in which marked pocketing is shown and large amounts of foul purulent sputum are raised.

In each of these four types, strong evidence of allergy was found. The authors report one case of each type in detail. On the basis of their observations on all these stages of bronchiectasis and the fact that the majority of patients had accompanying manifestations of allergy, the authors feel that most bronchiectasis is caused primarily by basal allergic bronchitis. It is considered preventable, therefore, if the basal allergic bronchitis is recognized as such and given intensive treatment before bronchiectasis develops. They further state that, even after bronchiectasis has developed, the disease may be successfully combated if treated early.

Upon allergic investigation it was found that most patients were sensitive to inhalants but in a few cases foods were the most important. Improvement was in proportion to the advancement of the disease. The development of bronchiectasis is explained on the following basis: first, there is a basal allergic bronchitis, second, an atelectasis, and third, in a variable length of time, the bronchiectatic dilatation.

Aphthous stomatitis and canker sores have long been known as possible manifestations of allergy. More recently, certain cases of gingivitis have been recognized by the dentist as of allergic origin. Gingivitis not infrequently occurs from dentifrices.

Loveman[24] reports an interesting case of stomatitis of the contact type. The lesions were confined mostly to the area surrounding an artificial denture. Marked positive patch tests were obtained to the cream which the patient used in cleaning the denture. The active ingredient in the cream was found to be anethol. Dermatitis was also

present on the left hand in which the denture was usually held in the process of cleaning. Passive transfer of the sensitivity was unsuccessful.

The cutaneous lesions of allergic purpura are not infrequently encountered in association with gastrointestinal lesions. Lesions of the upper digestive tract, however, are comparatively rare.

Three very interesting cases of purpura with faucial lesions were reported by Watson-Williams.[25] In two instances the lesions followed the administration of novarsenobenzol. In the first patient there was bleeding from both sides of the nasal septum. On the posterior wall of the pharynx there was a large purple bulla with bleeding edges. There was also bleeding from the tonsillar fossae. By endoscopic examination lesions were noted in the esophagus. A few purpuric spots were also seen on the extremities. Recovery followed discontinuation of the drug treatment.

The second patient showed a violet-black staining of the mucosa of the anterior faucial pillars, the gum margins adjacent to the teeth in both jaws, and the inner surface of both cheeks opposite the molars. There were no cutaneous lesions in this case. The patient recovered after discontinuation of the injection of novarsenobenzol.

The third patient had purpuric lesions of the nose, mouth, and pharynx. She also had some purpuric skin lesions of the chin and neck. The purpura in this case followed the ingestion of "aspro" tablets. The faucial lesions were very extensive. The patient completely recovered.

Lesions of the nervous system secondary to serum reactions have been noted to involve most frequently the brachial plexus. While lesions of the central nervous system may also occur, peripheral nerve lesions are the most common. Practically all of the cranial nerves have been reported as involved as isolated individual lesions. A very interesting case of recurrent paralysis of the larynx following the injection of tetanus antitoxin was reported by Neffson.[26] The patient was a male, aged 19 years, who, after the injection of 1,500 units of tetanus antitoxin developed first an urticaria, later generalized muscular and articular pains, and then suddenly a hoarseness. Examination of the larynx showed a complete paralysis of the left vocal cord and diminution of sensation on the left side of the larynx. The left pupil was slightly larger than the right. There was also an equivocal Babinski sign on the left, and questionable paresis of the right side of the face of central origin. The laryngeal paralysis improved gradually and disappeared completely three months after the onset.

In the following case, the serum reaction was characterized by involvement of the mucosa of the larynx rather than the laryngeal nerves. Taquino[27] reported the occurrence of laryngeal stenosis following the administration of tetanus antitoxin. The patient was a boy, 13 years of age, who had received an injury for which tetanus

antitoxin was administered in large doses over a period of about seven days. About a month after the last administration of tetanus antitoxin, the patient developed respiratory difficulty which required tracheotomy. Examination of the larynx made about six weeks later showed a marked hyperplasia and thickening of the ventricular bands.

REFERENCES

1. Jones, J. W.: Dermatitis Venenata From Use of Physostigmine Salicylate in the Eye, Arch. Dermat. & Syph. **37**: 82, 1938.
2. Simon, F.: Allergic Conjunctivitis Due to Fungi, J. A. M. A. **110**: 440, 1938.
3. Prewitt, L. H.: Retinal Detachment Due to Allergy, Arch. Ophth. **18**: 73, 1937.
4. Gray, I., and Walzer, M.: Studies in Mucous Membrane Hypersensitiveness, Am. J. Digest. Dis. **4**: 707, 1938.
5. Daly, S.: Lysozyme of Nasal Mucus. Method of Preparation and Preliminary Report on Its Effect on Growth and Virulence of Common Pathogens of Paranasal Sinuses, Arch. Otolaryng. **27**: 189, 1938.
6. Buhrmester, C. C.: Further Studies in the Hydrogen Ion Concentration of Nasal Secretions, Arch. Otolaryng. **27**: 83, 1938.
7. Abramson, H. A.: Tannic Acid Therapy in Allergy of the Nasal Mucosa, New York State J. Med. **37**: 1919, 1937.
8. Fishof, Frank E.: Treatment of Vasomotor Rhinitis and Allied Conditions With Sodium Morrhuate. Preliminary Report, Arch. Otolaryng. **27**: 413, 1938.
9. Hollender, A. R., and Fabricant, Noah: Nasal Ionization. Histologic Studies in Relation to Clinical Evaluation, Arch. Otolaryng. **27**: 452, 1938.
10. Hansel, F. K.: Status of Ionization in Nasal Allergy, Arch. Phys. Therapy **19**: 489, 1938. Reprinted in Eye, Ear, Nose & Throat Monthly, December, 1938.
11. Swann, C. C.: Allergy as Related to Otolaryngology, Arch. Pediat. **53**: 730, 1936.
12. Eyermann, C. H.: Food Allergy as a Cause of Vasomotor Rhinitis, South. M. J. **31**: 210, 1938.
13. Winkenwerder, W. L., and Gay, L. N.: Perennial Allergic Rhinitis. An Analysis of 198 Cases, Bull. Johns Hopkins Hosp. **61**: 90, 1937.
14. Hansel, F. K.: The Diagnosis of Nasal Allergy and Its Relation to Other Manifestations, South. M. J. **31**: 1003, 1938.
15. Semenov, H.: The Surgical Pathology of Nasal Sinusitis, J. A. M. A. **111**: 2189, 1938.
16. Ramirez, M. A.: Bronchial Asthma and Nasal Allergy, Arch. Otolaryng. **28**: 199, 1938.
17. Weille, F. L.: Studies in Asthma. The Nose and Throat in 500 Cases of Asthma, New England J. Med. **215**: 235, 1938.
18. Pollak, B. S., Cohen, S., and Gnassi, A.: Inflammatory Bronchial Tumors. Report of a Case and Review of the Literature, Arch. Otolaryng. **27**: 426, 1938.
19. Viswanathan, R.: Incidence of Bronchiectasis in Asthma, Indian M. Gaz. **73**: 138, 1938.
20. Walsh, T. W., and Meyer, O. O.: Coexistence of Bronchiectasis and Sinusitis, Arch. Int. Med. **61**: 890, 1938.
21. Goodale, R. L.: Analysis of 75 Cases of Bronchiectasis From the Point of View of Sinus Infection, Ann. Otol., Rhin. & Laryng. **111**: 347, 1938.
22. Watson, S. H., and Kibler, C. S.: New Conception of Bronchiectasis: Preliminary Report, Southwestern Med. **21**: 428, 1937.
23. Watson, S. H., and Kibler, C. S.: Bronchiectasis. A New Conception of Its Etiology Which Makes Prevention and Recovery Possible, J. A. M. A. **111**: 394, 1938.
24. Loveman, A. B.: Stomatitis Venenata, Arch. Derm. & Syph. **37**: 70, 1938.
25. Watson-Williams, E.: The Faucial Lesions of Purpura, J. Laryng. & Otol. **53**: 181, 1938.
26. Neffson, A.: Recurrent Paralysis of the Larynx Following Injection of Tetanus Antitoxin. Report of a Case, Arch. Otolaryng. **27**: 201, 1938.
27. Taquino, G. J.: Laryngeal Stenosis Following Tetanus Antitoxin, South. M. J. **31**: 88, 1938.

Selected Abstracts

Asthma and Hay Fever

UNDER THE DIRECTION OF SAMUEL M. FEINBERG, M.D., CHICAGO

Treatment of Intractable Bronchial Asthma by Bilateral Resection of the Posterior Pulmonary Plexus. Reinholf, W. F., Jr., and Gay, L. N.: Arch. Surg. **37:** 456, 1938.

Bilateral resection of the posterior pulmonary plexus was tried in 11 patients with repeated status asthmaticus. All of these individuals had been observed for long periods and had failed to obtain relief from the customary procedures. The aim of the operation is the complete separation of the lungs from the extrinsic autonomic supply. Both vagus and sympathetic tracts converge to form a small plexus on the posterior surface of the hilus, hence by thorough resection of this plexus complete isolation of the lung from any nervous influence may be produced. The operation is done in two stages. Following the first stage the asthma continues to recur but less severely than before and more readily controlled by epinephrine or atropine. Following the second stage there is even greater improvement with complete cessation of the attacks in some. There is a striking disappearance of emphysema.

The patients were followed for a period varying from 1¾ to 3¾ years. At the end of that time 4 were completely well; 4 had occasional mild attacks readily controlled by adrenaline; 1 improved for three months, then died from what appeared to be cardiac failure; 1 died several weeks after the operation from cerebral hemorrhage, and 1 patient was entirely unimproved.

Vasomotor Rhinorrhea With Asthma, Associated With Menstruation. Hoseason, A. S.: Brit. M. J. 2: 703, 1938.

The author cites two instances illustrating the effect of the premenstrual and menstrual changes on the nasal mucosa. Typical vasomotor rhinorrhea, and even asthma, may occur. He believes that the cases can be treated by dealing with the "final common path," the nose. This he does by means of intranasal zinc ionization.

Seasonal Aspects of Asthma and Hay Fever in New England With Special Reference to Sensitivity to Mold Spores. Pratt, H. N.: New England J. Med. **219:** 782, 1938.

Pratt analyzes the importance of mold spores in the production of respiratory allergic symptoms in the Boston area. He studied the air spore content by exposure of Petri plates of Sabouraud's medium for thirty minutes daily since February 1, 1937. The most common colonies found on the plates were those of *Alternaria, Hormodendrum, Aspergillus, Penicillium,* and *Chaetomium,* with the first two varieties assuming a more seasonal prevalence. The points in the history of patients leading the author to suspect mold allergy were the increase of symptoms during the summer months, the marked symptoms between the grass and ragweed

seasons, the tendency to persistence of symptoms between the first frost and the time of blanketing of the ground with snow, and finally the practically complete absence of symptoms during January and February. The extracts were prepared as follows: The mold was grown for about a month in a flask containing about 50 c.c. of liquid Sabouraud's medium and then ground directly in the remaining liquid. After Seitz filtration and addition of phenol, the undiluted liquid was used for intracutaneous testing. Of 177 children suffering from asthma or hay fever who were thus tested, 25 per cent reacted to *Alternaria*, 6 per cent to *Hormodendrum*, 4 per cent to *Aspergillus*, and 2 per cent to *Penicillium*. Passive transfer reactions were obtained in the majority of those tried. During 1937, 34 of these patients suffering from seasonal hay fever or asthma were treated with mold extracts, with or without the addition of pollen treatment. Many of these had been treated in previous seasons with pollen extracts alone with poor results. Of these 34 patients, 28 obtained either good or fair results. The author concludes that treatment with graded doses of mold extract in specifically sensitive individuals is as effective as pollen therapy in pollen-sensitive patients.

Subcutaneous Emphysema With Asthma. Van Fleet, H. D., Miller, H., and Scott, A. J.: California & West. Med. **49**: 265, 1938.

The authors add four additional cases of subcutaneous emphysema due to asthma to those previously reported by others. The patients were a 5-year-old boy having asthma for three and one-half years; a 10-year-old girl having asthma for two and one-half years; a 19-year-old girl having asthma for two years, and a 28-year-old man suffering with asthma for twenty-one years. All patients recovered and the air was absorbed within ten days.

Concerning the Differentiation Between Bronchial Asthma vs. Cardiac Disease, and Possible Ill Effects From the Administration of Excessive Amounts of Epinephrine in the Former Condition. Smith, F. M., and Paul, W. D.: Ann. Int. Med. **12**: 585, 1938.

The authors stress the importance and difficulties in the differentiation between bronchial asthma and cardiac disease. This applies to three groups of cases. Those who have had asthma for many years, with resulting emphysema, who have reached the age in which degenerative disease of the heart is common, offer a diagnostic problem. When the onset of asthma occurs late in life, the possibility of an allergic asthma may still be present. It also happens that some individuals will have a chronic asthma with a concomitant cardiac disease, hence the causative factor of the asthma will be often puzzling. The authors feel that the experimental and clinical observations indicate that epinephrine may do harm in the cardiac types of asthma, or in those cases of bronchial asthma in which associated cardiac damage exists. They concur in the findings of others regarding the efficacy of intravenous injections of theophylline ethylenediamine in such instances.

Dermatology

UNDER THE DIRECTION OF JOSEPH GOODMAN, M.D., BOSTON

Cement Eczema. An Experimental and Clinical Study. Burckhardt, W.: Arch. f. Dermat. u. Syph. **178**: 1, 1938.

Eighty patients with cement eczema and 100 control patients with no skin disease were studied by means of patch tests to various cements and individual components

of cements (calcium hydroxide, di- and tricalcium silicate, di- and tricalcium aluminate). It was found that reactions to these materials could be produced in all eczema patients and in all control patients, but that the eczema group showed reactions to lower concentrations of the materials tested than did the control group. This was particularly true of the reactions to calcium hydroxide. The threshold of the patch test reaction to cement and to components of cement (that is, the lowest concentrations of the substances to which the individual reacted) was found to run parallel to the ability of the individual's skin to neutralize alkali. In other words, the faster the individual neutralized alkali applied to the skin, the higher the concentration of the tested substances required to produce a patch test reaction.

In 90 per cent of the patients with cement eczema no evidence of allergic hypersensitivity to cement or components of cement was found. In 10 per cent (8 individuals) truly eczematous patch test reactions were found. Seven of these patients showed evidence of seborrheic eczema or some other form of eczema in addition to the cement eczema. The possibility remains, therefore, that these reactions were an isomorphic effect (Köbner phenomenon) and did not indicate true allergic hypersensitivity to the substances tested. In the one remaining patient the evidence indicated the presence of an allergic hypersensitivity to alkali or to substances produced by the action of alkali on the skin.

Patch tests with substances which commonly cause contact dermatitis were for the most part negative in patients with cement eczema. However, microscopically and macroscopically these patients reacted to calcium chloride in the same manner as to cement. The author concludes that exposure to cement produces eczema in those individuals whose skins neutralize alkali slowly, that the exposure to alkali is the main factor in the production of the eczema, but that in all likelihood the calcium ion, present in high concentration in all cements, plays a part. Not only substances which produce allergic reactions, but also those which, like cement, produce banal toxic reactions can produce in the skin the conditions necessary for the development of chronic eczema.

A discussion of the clinical aspects of cement dermatitis is also included in the paper.

Experimental Investigation of Photosensitization of the Skin by Plant Substances. Kuske, Hans: Arch. f. Dermat. u. Syph. **178**: 112, 1938.

The author tested the juice expressed from the leafy parts of various plants for their ability to photosensitize. Material from *Ruta graveolens, Ficus carica,* and *Heracleum mantegazianum* was found to be extremely potent in producing sensitization. Since the nature of these plants suggested that furocumarines (complex organic substances containing lactone groupings) might be responsible for this photosensitization, two such substances were prepared for testing: bergapten, from the residue left after distillation of oil of bergamot, and oxypeucedanin, from the root of *Peucedanum ostruthium.* Both were found to produce a high degree of photosensitization when application to the skin was followed by a few minutes' exposure to natural or to certain artificial lights.

The skin reaction appeared seven to twelve hours after the first or subsequent application of the photosensitizer. Only the areas to which the substances were applied showed a reaction, which consisted (depending on the amount of exposure to light) of erythema, edema, and bullae. Intense pigmentation followed the reactions and disappeared very slowly.

Comparative Study of the Tuberculin Patch Test and the Mantoux Intracutaneous Test. Vollmer, H., and Goldberger, E. W.: Am. J. Dis. Child. **56**: 584, 1938.

In these studies the tuberculin used for patch testing was about four times as strong as the usual old tuberculin used for the Mantoux test. Tests were done on 169 tuberculous children, of which number 164 reacted positively both to the patch test and to a Mantoux test with the first strength of purified protein derivative. One subject did not react to the purified protein derivative, but gave a positive reaction to the patch test. The remaining 4 subjects were negative to both the intradermal test and the patch test. A repeat of the patch test and an intradermal test with the second strength of purified protein derivative resulted in entirely negative reactions in 2 patients and positive reactions in the remaining 2, one of which also showed a positive patch test. In only one instance in this series, then, did the patch test fail to produce a reaction in an individual who reacted to intradermal testing with purified protein derivative, second strength.

In a series of 118 children admitted to a pediatric ward there were 12 reactions to the tuberculin patch test. Of these 12, 8 had positive Pirquet tests, 2 had questionably positive Pirquet tests, and 2 had negative Pirquet but positive Mantoux tests.

Cellular Reactions to Tuberculo-Proteins Compared With the Reaction to Tuberculo-Lipids. Sabin, F. R.: J. Exper. Med. **68**: 837, 1938.

The cellular reaction to tuberculophosphatide and so-called waxes prepared from the tubercle bacillus, after intradermal or intraperitoneal injection into guinea pigs, was found to be relatively simple and uniform. First, there was a multiplication of monocytes, then fusion of these cells to form foreign body giant cells, and lastly, disintegration of the inert lipid material within the giant cells. On the other hand, similar injections of various tuberculoproteins produced much more complex reactions, consisting of monocytes, stimulated monocytes, macrophages, epithelioid cells singly and in tubercles, and giant cells, both of the Langhans and of the foreign body type.

A comparison of the cellular reactions of normal and tuberculous animals revealed that tuberculoprotein in solution induced the formation of monocytes in the normal, and of epithelioid cell tubercles in the tuberculous animal. Freshly precipitated tuberculoproteins induced a moderate formation of epithelioid cells in normal animals, and more in the tuberculous. Insoluble forms of tuberculoprotein induced complex tubercular tissue both in normal and in tuberculous animals. However, the reaction was more marked in the latter.

Cellular Reactions to Defatted Tubercle Bacilli and Their Products. Sabin, F. R., and Joyner, A. L.: J. Exper. Med. **68**: 853, 1938.

Intradermal and intraperitoneal injection into rabbits and guinea pigs of defatted tubercle bacilli (the second residue of Anderson), and the material remaining after alcohol extraction of this residue (the third residue of Anderson) gave rise to cellular reactions which were much like those known to characterize the reaction to heat-killed tubercle bacilli. These reactions consisted of abscesses, tubercles of monocytes and epithelioid cells, monocytes diffusely scattered in the tissues, and giant cells, many of which contained acid-fast bacilli. Removal of firmly bound lipid from the third residue produced a relatively inert fourth residue, which, however, still retained the property of stimulating a new formation of monocytes. The firmly bound lipid contained an hydroxy-acid and a polysaccharide. The former gave rise to foreign body giant cells, with subsesequent eosinophilic infiltration, whereas the latter resulted in an infiltration of neutrophiles from the blood stream.

Immunology

UNDER THE DIRECTION OF MATTHEW WALZER, M.D., BROOKLYN

Antigenic Qualities of Antitoxins. Weil, R. J., Parfentjev, I. A., and Bowman, K. L.: J. Immunol. **35:** 399, 1938.

The authors report their studies on the nature of the difference between normal globulin and immune globulin.

A solution of modified globulin very rich in antibody, obtained by a special method of partial peptic digestion of immune sera, was used. The antigenic property of antitoxic globulin thus obtained was compared with that of normal and of immune horse sera, as well as of antitoxic globulin that was salted out in the usual way with ammonium sulfate. Diphtheria antitoxin, staphylococcal antitoxin, and antitoxin of *B. welchii* were used in most of the experiments performed on rabbits, guinea pigs, and men. The methods of testing included precipitin tests, complement fixation, and tests for cutaneous hypersensitiveness. A method of comparison, devised by one of the authors, was used to estimate the relative concentration of the same antigen in two solutions.

The reported experiments demonstrate that the antigenic qualities of antisera modified by partial peptic digestion are markedly impaired. The activity of the modified globulin when tested on the skin of naturally or passively sensitized human beings is about 0.002 that of unaltered globulin. The writers conclude that a small fraction of unmodified protein, present in the modified globulin, accounts for the residual antigenic activity. They call attention to the fact that unimpaired antibody function exists in the digested preparations.

On the Cause of Liquefaction of the Collagenous Fibers in Hyperergic Inflammation (Arthus Phenomenon). Werner, M.: Virchows Arch. f. path. Anat. **301:** 552, 1938.

The author studied the pathology of the Arthus phenomenon to determine whether the swelling and liquefaction of the collagenous fibers, so typical of the histologic picture of this reaction, are pathologically specific for this phenomenon.

Rabbits were sensitized by subcutaneous injections of sheep serum until an Arthus reaction developed. Thorough studies were made of the pH of the tissues because of its importance in the production of tissue edema. The effect of the subcutaneous injection of various substances on the nonspecific production of edema in sensitized rabbits was also studied.

The writer confirmed the morphologic picture of the Arthus phenomenon as described by Arthus and Breton. Determinations of the tissue pH did not reveal the presence of tissue acidosis, which might have been responsible for the edema at the Arthus site. The histologic picture of swelling and liquefaction of the collagenous fibers, described as occurring specifically in the hyperergic reaction, was shown to be independent of the specific antigen-antibody reaction, and thus not specific for the hyperergic reaction.

The Antiallergic Effect of Insulin Shock and Liberation of Histamine. Barthelheimer, H., and Afendulis, H.: Ztschr. f. d. ges. exper. Med. **104:** 31, 1938.

In a previous communication the authors reported their experiments on the antianaphylactic action of insulin shock in sensitized guinea pigs. In the present investigation the writers attempted to determine whether this antianaphylactic effect was due to the hormone characer of the insulin or to a nonspecific desensitization.

Guinea pigs were sensitized by two injections of 0.5 c.c. of horse serum. These animals then received biweekly injections of 10 units of insulin for five weeks. Insulin shock was prevented by the simultaneous administration of glucose. Several animals were given inactivated insulin. In all instances acute anaphylactic shock occurred within five minutes following the intravenous injection of the shocking dose of 0.6 c.c. of horse serum. The authors concluded that the antianaphylactic effect of insulin was thus shown not to be due either to the hormone character or to the protein content of insulin.

In further experiments the authors demonstrated that there is a demonstrable amount of histamine liberated during insulin shock. They believe that the repeated liberation of histamine by insulin shock in sensitized guinea pigs is responsible for the antianaphylactic effects observed.

Chemo-Immunological Studies on Conjugated Carbohydrate—Proteins. XII. The Immunological Properties of an Artificial Antigen Containing Cellobiuronic Acid. Goebel, W. F.: J. Exper. Med. **68**: 469, 1938.

In order to understand more fully the role which the aldobionic acids, the fundamental building stones of certain bacterial polysaccharides, play in immunologic phenomena, the author has studied the immunologic properties of the antigens, cellobiose, and cellobiuronic acid containing these acids.

Immunizing antigens were prepared by combining the diazotized p-aminobenzyl-beta glycoside of glucose, glucuronic acid, cellobiose, and cellobiuronic acid with the globulin fraction of normal horse serum. Rabbits were immunized by two or three courses of six daily intravenous injections of 5 mg. of antigen dissolved in sterile physiologic salt solution. Seven days after the last injection the animals were bled. In order to avoid cross reactions the test antigens used in the serologic analysis (precipitin reactions, inhibition of precipitin reactions) were prepared by combining the diazonum derivatives of the various glycosides to the protein of chicken serum.

The artificial antigens containing the azobenzyl glycosides of the disaccharide cellobiose and the aldobionic acid, cellobiuronic acid, gave rise in rabbits to antibodies which are specific and characteristic of the saccharide constituent. The antiserum to cellobiuronic acid showed broader serologic cross reactions than did that to cellobiose, reacting not only with the disaccharide antigen, but with simple glucose and glucuronic acid antigens as well. An antiserum to the cellobiuronic acid antigen precipitates the capsular polysaccharide of type III pneumococcus, when the latter is combined with egg albumen, and conveys passive protection on mice to infection with virulent pneumococcic types II, III, and VIII.

The functional role of acid groups in determining certain of the serologic characteristics of bacterial polysaccharides is affirmed by the results of the present study.

Effect of Splenectomy on Response to Pituitary Material and the Question of the Antihormone. Gordon, A. S., and Charipper, H. A.: Proc. Soc. Exper. Biol. & Med. **38**: 773, 1938.

The authors present an excellent discussion on the question of antihormone. One of the strongest arguments in favor of the antibody-like nature of these antagonistic substances has been the failure of animals receiving treatment with pituitary hormones of the same species to become refractory, or to develop antihormone substances. In previous papers, the authors reported that the reticulo-

endothelial system, known to be concerned with the production of antibodies, is intimately related to the state of refractoriness which develops after prolonged treatment with heterozoic endocrine extracts.

As a result of the present investigation, which deals with the effect of injections of homozoic and heterozoic pituitary material in normal as compared to splenectomized animals, the authors conclude that splenectomy in rats is without effect on the ovarian and uterine weight response to injections of homozoic pituitary material. Splenectomized rats, however, show greater response when treated with pituitary material from a heterozoic source than similarly treated controls. This, according to the writers, lends further support to the contention that the state of refractoriness, which develops after prolonged treatment with hormone preparations, is immunologic in nature.

Pediatrics

UNDER THE DIRECTION OF WILLIAM C. DEAMER, M.D., SAN FRANCISCO

Allergy in Childhood: Prophylaxis, Early Recognition and Treatment. McGee, W. A.: J. A. M. A. **111:** 1551, 1938.

The author reviews the measures which attempt to prevent intrauterine sensitization and sensitization early in life, including attention to the mother's diet, avoidance of likely food allergens in the infant's diet, and environmental control in the nursery. Numerous signs and symptoms of allergy which are not usually recognized as such are mentioned, including circumoral pallor, night sweats, subocular discoloration, colitis, and constipation. He favors intracutaneous tests and finds elimination diets of limited value "since it takes a period from days to several weeks to eliminate foods causing clinical allergy." It is often not possible or practical to eliminate inhalant allergens, and therefore inhalant desensitization is recommended.

Contact and Environmental Allergens as a Cause of Eczema in Infants and in Children. Osborne, E. D., and Walker, H. L.: Arch. Dermat. & Syph. **38:** 511, 1938.

Patch tests to various chemicals and medicaments in 94 normal newborn infants were uniformly negative. In a follow-up two years later 71 of the 94 original cases were examined. Four had had eczema, and in all four ammoniated mercury ointment appeared to be the causative factor. It is thought that the routine use of this ointment in preventing impetigo in the newborn predisposes the infant to subsequent eczema from mercury preparations and other substances as well.

In attacking the problem of eczema the authors find routine scratch and intradermal tests and elimination diets entirely inadequate. They feel that routine patch tests are not much better. They find actual clinical trial, as with a wool coat or feather pillow, more informative. The patch test often fails because it does not simulate clinical conditions of moisture, abrasion, and so on.

In 124 cases of eczema in infants and children attention to contact and environmental allergens cured 50 per cent and improved another 35 per cent. Food allergens do not account for more than 15 or 20 per cent of cases, and sensitization to contact and environmental allergens is the greatest single factor. Transepidermal absorption of water-soluble protein is common and can be shown by a flare-up of old eczema sites by a patch test which may itself remain negative.

Concerning the Simultaneous Appearance of Asthma and Eczema and Their Reciprocal Relationship in Children. Casper, F. J.: Arch. f. Kinderh. **115**: 95, 1938.

After discussing the viewpoint that asthma and eczema depend on a common constitutional basis, the author seeks in addition a common factor capable of eliciting the symptoms of these diseases. He finds this in the concept of altered histamine metabolism. He emphasizes the frequency of the observation that one disease influences the other favorably, and suggests that the offending substance, histamine, may be fixed either in the skin or in the lung, thus removing it as a source of further irritation.

Practical Points in the Interpretation of the Allergy Skin Tests. Stoesser, A. V., and Greenberg, R.: Journal-Lancet **58**: 482, 1938.

Only about one-fourth or less of the positive food reactions have clinical significance in eczema and asthma. However, among the asthmatics a history of eczema makes for a much higher percentage of reactions without clinical significance than is the case with asthmatics who have not had eczema.

Group testing intradermally has led to numerous irritation reactions not present with any single component of the group.

Human Passive Transfer Antibody. IV. Studies on Children Hypersensitive to Foods. Lippard, V. W., and Schmidt, W. M.: Am. J. Dis. Child. **56**: 797, 1938.

Having previously demonstrated a rise in antibody following pollen therapy in sensitive individuals, the authors applied their method to a study of the antibody titer following ingestion of a specific food in sensitive individuals. Four children were studied in detail. An increase in antibody was shown to occur usually after the ingestion of sufficient antigen to cause clinical symptoms. After this rise in antibody titer, clinical reactions to ingestion of the specific foods were either absent or much less pronounced. As previously, the observations suggested that in human beings protection of sensitized tissues from manifestations of hypersensitiveness may be associated with a rise in titer of circulating antibody. They feel that the antibody concerned and determined by their method is the passive transfer antibody.

Rhinology and Ophthalmology

UNDER THE DIRECTION OF FRENCH K. HANSEL, M.D., ST. LOUIS

The Role That Surgery of the Paranasal Sinuses Plays in the Asthmatic Child. Creasy, R. C.: Laryngoscope **48**: 415, 1938.

The role that surgery of the paranasal sinuses plays in the asthmatic child was investigated in a group of 60 children between the ages of 5 and 14 years. In 5 patients there were slight veiling or edematous change shown in the x-ray plates. Eight of the cases showed membranous antritis. In 21 there was combined antritis and ethmoiditis. Of these 21 patients, 7 had antritis and ethmoiditis on the left side, and in 14 the same process was on the right side. Five patients showed bilateral ethmoiditis with involvement of one antrum. Seven had bilateral antritis, 6 had bilateral antritis and ethmoiditis, and 2 had pansinusitis. It is significant that in this group of 60 cases there were three males to each female.

The results were reported as follows: 15 patients were asymptomatic after two years; 33 were asymptomatic from one to three months. In three patients no results were attributed to poor cooperation, and in 6 the degree of improvement was not stated. Among the complications of the surgical procedures, one patient had bilateral mastoiditis, one had scarlet fever with postscarlet mastoiditis, one had pyelitis, and 4 had acute otitis media requiring myringotomy.

The author does not state the total number of cases from which these patients were selected. The incidence of pathologic changes reported, therefore, is unknown. Cytologic studies of secretion apparently were not made, at least it was not stated that this laboratory procedure was utilized, in diagnosis or in determining the presence of infection. The diagnosis of sinus infection in cases of asthma certainly cannot be based upon the x-ray plates without the correlation of cytologic examinations. It is significant that an undue number of complications followed the instituted surgical procedures.

Bronchoscopy in Bronchial Asthma. Andrews, A. H., Jr.: Illinois M. J. **73**: 25, 1938.

Andrews states that bronchoscopy in bronchial asthma is valuable as a diagnostic aid, and that bronchoscopic aspiration has definite therapeutic effectiveness. It is a means of obtaining secretions for the preparation of vaccines. He further states that bronchoscopy is of diagnostic value in bronchial asthma because it is a means of determining the type of tracheobronchial changes and of differentiating asthma from other conditions. He found that vaccines prepared from bronchoscopically aspirated secretions were more satisfactory than ordinary sputum vaccines. In certain cases definite improvement followed the aspiration of secretions. He feels, however, that bronchoscopic therapy is a symptomatic method of treatment and is only an adjunct to allergic management.

Andrews makes no reference to the cytologic study of the secretions from the tracheobronchial tree. In studies of this type the cytologic examination of the secretions should be correlated with other findings. In certain cases accurate diagnosis may be dependent upon cytologic findings entirely.

Ionization of Allergic Rhinitis. King, E. D.: Arch. Phys. Therapy **19**: 645, 1938.

The results obtained in nasal ionization in 72 cases of hay fever were reported by King. Among 24 patients with autumnal hay fever, 4 had complete relief, 9 were improved, and 11 had no relief. In 19 patients with spring hay fever, 5 had complete relief, 10 showed improvement, and 4 obtained no benefit. Among 32 patients with perennial nasal allergy, 6 were relieved, 14 were improved, and 12 had no relief. In summarizing the entire group, it is significant that 15 patients had relief, 33 improved, and 27 had no relief.

The Sinuses as Points of Focal Infection and the Treatment of Sinusitis. Fletcher, W.: Laryngoscope **48**: 17, 1938.

In discussing the subject of sinus disease in general, Fletcher enumerates such complaints as sneezing, profuse discharge, and nasal obstruction among other symptoms, such as headache, pain, and fever. He further states that the formation of polyps is the result of long-continued infection. He also remarks that infection from the sinuses may spread to the tonsils and adenoids. He defines acute sinus infection as simply a "cold in the head" and chronic sinus disease as "catarrh." An infection is mentioned as the usual cause of disease.

A comprehensive discussion on the general subject of sinus disease certainly cannot exclude the consideration of allergy.

Miscellaneous

Migraine From the Allergic Point of View: Results of Treatment in 105 Cases. Spees, C.: M. J. Australia **1**: 875, 1938.

The author discusses allergic migraine in a conventional way and distinguishes between cases due to foods and those secondary to nasal allergy. He establishes an initial diet from intracutaneous reactions and considers doubtful and delayed reactions as positive. These tests agreed closely with clinical observations. The leucopenic index was used and found helpful but time consuming. Elimination of offending foods, supplemented by peptone therapy when this was not possible, was followed by complete or partial relief in 84.8 per cent of his patients.

Some More or Less Recent Therapeutic Methods Used in Bronchial Asthma and Other Allergic Syndromes. Sangiorgi, P. I.: Quaderni Dell'Allergia **4**: 1, 1938.

The author describes various therapeutic measures used in his experiences for the relief of allergic disorders. These include aurotherapy. The gold salts thus administered were of various forms, most of them Italian commercial preparations. These preparations have been satisfactory in 40 cases, most of which were in younger individuals. Treatment with tuberculin, especially for asthma, has been used fairly extensively, beginning with very dilute solutions and continued for a year or more with weekly injections. Cases that did respond had lasting results. In some instances tuberculin therapy was combined with injection of gold salts. Treatment of asthma with insulin wherein a hypoglycemic crisis is induced is discussed. Theory of improvement is considered to be due to the stimulation of adrenin by the quick fall of blood sugar. Although insulin therapy seems to have a symptomatic effect, it is of no value otherwise. Histamine therapy is discussed, but from actual experience the author has had good results in only 3 of 16 cases, and 3 were made worse.

Neuritis Caused by Prophylactic Tetanus Serum. Meszaros, K.: Deutsche Ztschr. f. d. ges. gerichtl. Med. **30**: 45, 1938.

A review of neurologic manifestations after serum injections is given, and a case is cited. The patient developed signs of serum sickness eleven days after prophylactic tetanus serum administration. This was soon followed by weakness of the right deltoid, anterior serratus, latissimus dorsi, and infraspinatus muscles. This weakness persisted for nine months to the extent that he could not work during that time. Three other cases are cited wherein the sites of injection were remote from the parts affected. This complication of serum injection is rare and should not contraindicate its use. Recovery of nerve injury is usually complete within two years.

Erratum

On page 39 of the article by Romanoff entitled "The Effect of Testicular Extract (Reynals Spreading Factors) Upon Human Skin" in the November issue of the JOURNAL, the first line should read "0.02 c.c. of lamb extract" instead of "0.2 c.c. of lamb extract."